# UNIVERSITY OF SUSSEX

# STUDIES TOWARDS THE TOTAL SYNTHESIS OF (−)-KAINIC ACID AND ALLOKAINIC ACID.

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**A Thesis Submitted for the Degree of**

**Doctor of Philosophy**

**School of Life Science,**

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*I dedicate this thesis to my parents Veera Reddy and Pitchamma Panta, my brothers Mohan and Gurva, and my surrogate brother Dandeker Chandrakanth. Who have supported me all the way throughout my education in Univ of Sussex.*

I hereby declare that this thesis has not been submitted, either in the same or different form, to this or any other University for a degree.

**Signature:**

**Table of Contents**

# Acknowledgement

It is difficult to overstate my gratitude to my PhD supervisor, Prof. Philip J. Parsons. With his enthusiasm, inspiration, and his great efforts made things easy and look simple. It has been an honour to work with him and I am very grateful for his continued friendship.

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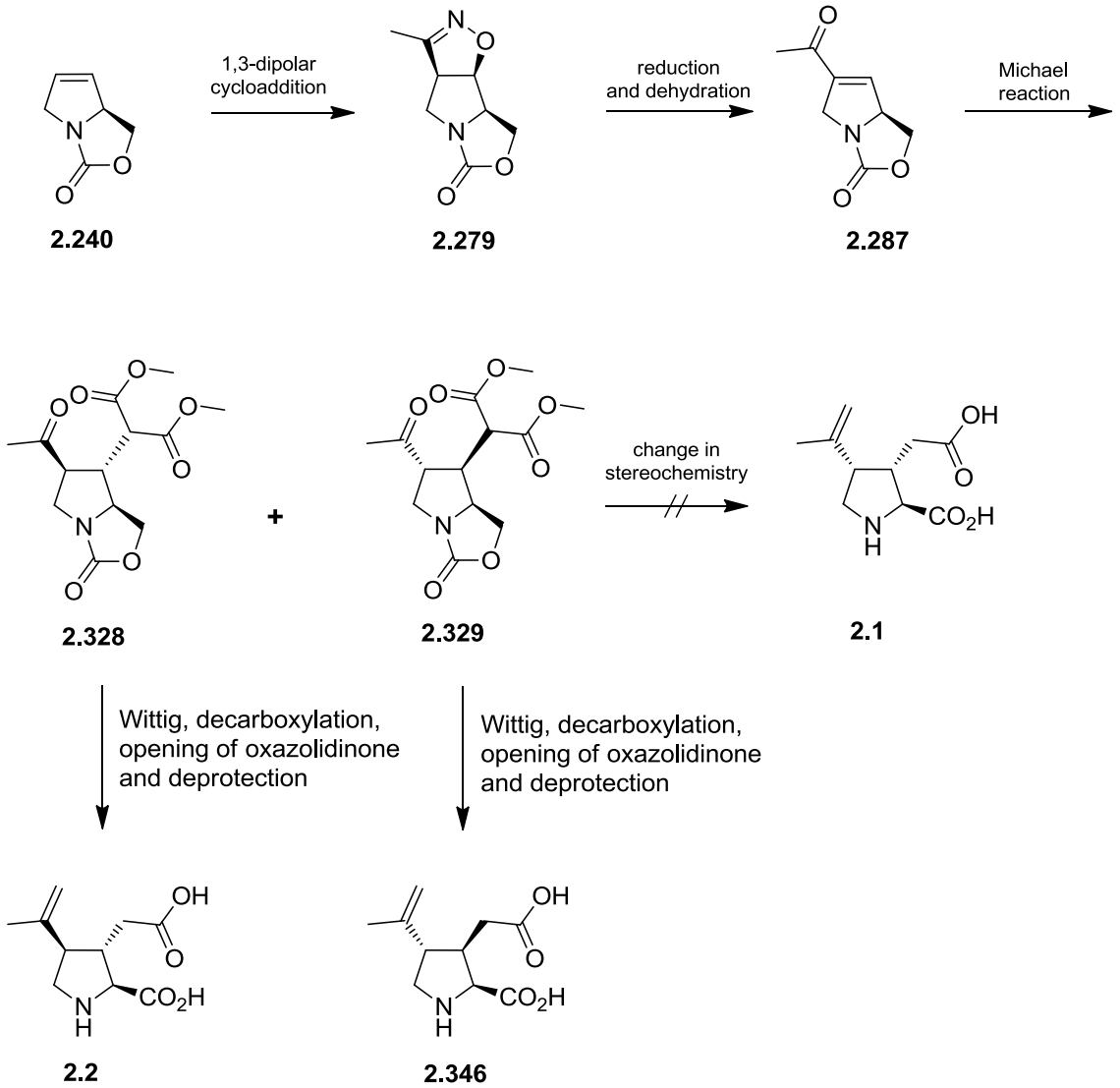
# Abstract

This study commenced with an investigation into a total synthesis of the antibiotic platensimycin **1.1** in chapter one. The key reaction for accessing the synthetically challenging fused ring system involved a *meta*-photocycloaddition reaction and the chapter one describes our attempts at the syntheses of the key substrates. Much of the chemistry was unsuccessful however we were able to attempt a key photochemical reaction however the desired compound was not obtained. On the basis of these outcomes we refocused our efforts towards the syntheses of kainic acid **2.1** and allokaininc acid **2.2** in chapter two.



We aimed to devise a stereoselective synthesis of both kainic acid **2.1** and the allokainic acid **2.2**, utilising the diastereofacial selectivity inherent in the previously synthesised oxazolidinone **2.240**. Oxazolidinone **2.240** was subjected to a stereo and regiocontrolled 1,3-dipolar cycloaddition to give isoxazole **2.279**. Reduction, followed by dehydration of isoxazole **2.279** gave the enone **2.287** which forms the Michael acceptor in the key Michael addition reaction. The 1,4 addition on enone **2.287**, gave the two diastereomers **2.328** and **2.329** which underwent sequential Wittig reaction, and Krapcho decarboxylation to give the formal synthesis of allokainic acid **2.2** and epikainate **2.346** respectively. An investigation was also conducted with the aim of altering the stereochemistry of the dicarboxylic group in compound **2.329**, in order to produce a novel route to the stereoselective synthesis of kainic acid **2.1**.

# Abbreviations

| | |
|---|---|
| Å | Ångstrom |
| Ac | acetyl |
| addn. | addition |
| AIBN | 2,2′-azobis(2-methylpropionitrile) |
| 9-BBN | 9-borabicyclo[3.3.1]nonane |
| Bn | benzyl |
| Boc | *tert*-butoxycarbonyl |
| Bu | butyl |
| $^{S}$Bu | *sec*-butyl |
| $^{t}$Bu | *tert*-butyl |
| $^{n}$Bu | butyl |
| Bz | benzoyl |
| $^{o}$C | degree celsius |
| CAN | ceric ammonium nitrate |
| cat. | catalytic |
| CDI | 1, 1'-carbonyldiimidazole |
| COD | 1,5-cyclooctadiene |
| conc. | concentrated |
| CPAA | 2-carboxy-3-pyrrolidine-3-acetic acid |
| *m*-CPBA | *meta*-chloroperbenzoic acid |
| Cp | cyclopentadienyl |

| | |
|---|---|
| DAST | *N*,*N*-diethylaminosulfur trifluoride |
| DBU | 1,8-diazobicyclo[5.4.0]undec-7-ene |
| DCM | dichloromethane |
| DEA | diethanolamine |
| DEAD | diethyl azodicarboxylate |
| DEPC | diethyl pyrocarbonate |
| DEPT | distortionless enhancement by polarization transfer |
| DIBAL | diisobutylaluminium hydride |
| DMAP | 4-dimethylaminopyridine |
| DMDO | dimethyldioxirane |
| DME | dimethyl ether |
| DMF | *N*,*N*-dimethylformamide |
| DMM | dimethoxymethane |
| DMP | Dess-Martin periodinane |
| DMS | dimethyl sulfide |
| DMSO | dimethyl sulfoxide |
| d.r. | diastereomeric ratio |
| EDTA | ethylenediaminetetraacetic acid |
| eq. | equivalents |
| Et | ethyl |
| ESI | electrospray ionization |
| FTIR | Fourier transform infrared spectroscopy |

| | |
|---|---|
| g | gram(s) |
| h | hour(s) |
| HOMO | highest occupied molecular orbital |
| HMPA | hexamethylphosphoramide |
| HRMS | high resolution mass spectrum |
| HSBM | high speed ball milling |
| HSQC | heteronuclear single quantum correlation |
| Hz | Hertz |
| IR | infrared spectroscopy |
| kbar | kilobar |
| KHMDS | potassium hexamethyldisilazide |
| LDA | lithium di-*iso*-propylamide |
| LHMDS | lithium hexamethyldisilazide |
| M | molar |
| Me | methyl |
| min. | minute(s) |
| mL | millilitre |
| mol | mole |
| mmol | millimole |
| m.p. | melting point |
| Ms | methanesulfonyl |
| M.S. | molecular sieve |

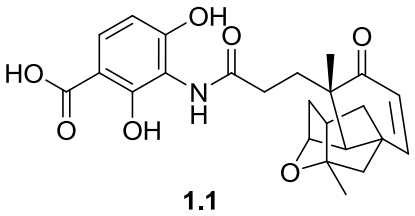
| | |
|---|---|
| MS | mass spectrometry |
| MW | microwave |
| MOM | methoxymethyl |
| NBS | *N*-bromosuccinimide |
| NIS | *N*-iodosuccinimide |
| NMO | 4-methylmorpholine *N*-oxide |
| NMR | nuclear magnetic resonance |
| Ph | phenyl |
| Piv | pivolyl |
| PMB | *p*-methoxybenzyl |
| PMP | *p*-methoxyphenyl |
| ppm | parts per million |
| PTSA | *para*-toluenesulphonic acid |
| $^{i}$Pr | *iso*-propyl |
| pyr. | pyridine |
| Rf | retention factor |
| RCM | Ring closing metathesis |
| rt | room temperature |
| TBS/TBDMS | *tert*-butyldimethylsilyl |
| TBDPS | *tert*-butyldiphenylsilyl |
| TES | triethylsilyl |
| TEA | triethanolamine |

| | |
|---|---|
| TFA | trifluoroacetic acid |
| THF | tetrahydrofuran |
| THP | tetrahydropyranyl |
| TIPS | triisopropylsilyl |
| TLC | thin layer chromatography |
| TMANO | trimethylaminoxide |
| TMS | trimethylsilyl |
| Ts | tosyl |
| UV | ultra violet |
| VAp | calcium vanadate apatite |
| VAp-hw | It was found that pretreatment with hot water of the VAp calcined at 800°C, abbreviated as VAp-hw. |
| w | watt |

# CHAPTER ONE

## 1.1. Introduction

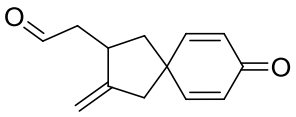
Platensimycin **1.1** is a novel broad spectrum Gram-positive antibiotic used in antibiotic research due to its unique functional pattern and significant antibacterial activity.[1,2]




**1.1**

**Figure 1.1:** Platensimycin.

According to Wang,[1] platensimycin demonstrates strong, broad-spectrum Gram-positive antibacterial activity by selectively inhibiting cellular lipid biosynthesis. This anti-bacterial effect is exerted through the selective targeting of *β*-ketoacyl-(acyl-carrier-protein (ACP)) synthase I/II (FabF/B) in the synthetic pathway of fatty acids. Treatment with platensimycin in mice eradicates *Staphylococcus aureus* infection.[1,2] The first total synthesis of platensimycin **1.1** has been published by K.C. Nicolaou which involves the syntheses of a key dienone intermediate **1.2** prepared using a multi-step procedure.[3]

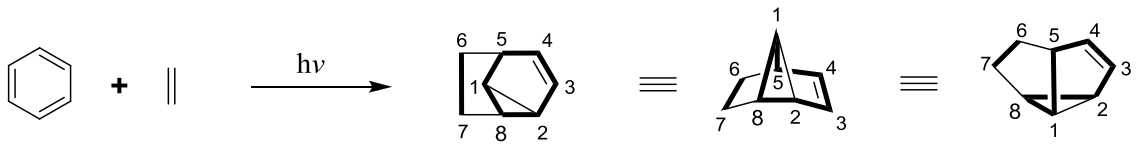



**1.2**

**Figure 1.2:** Nicolaou's dienone intermediate.

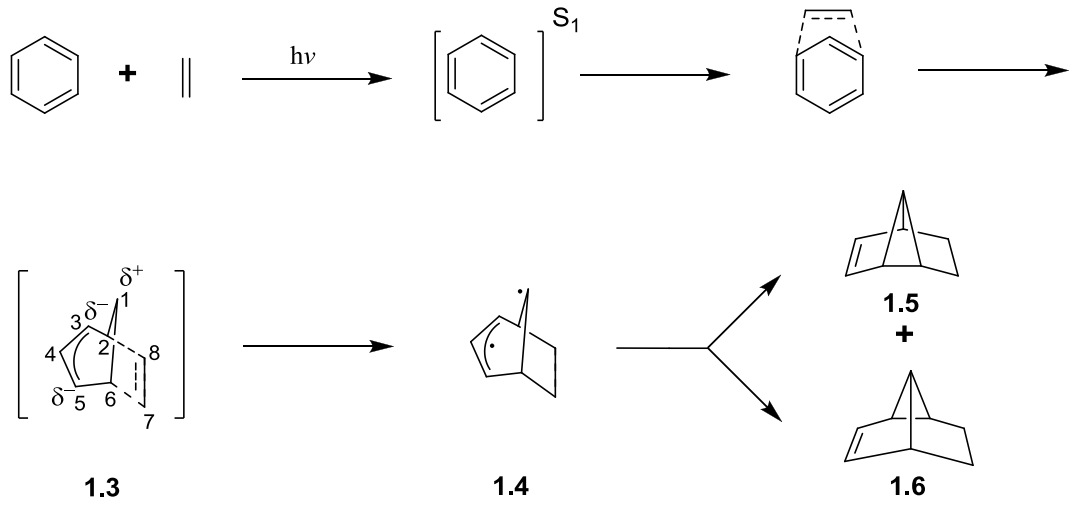
We developed two strategies for the synthesis of platensimycin **1.1** which are relatively short and will provide a range of analogues for biological screening. Both the strategies involve *meta*-photocycloaddition reaction[4]. The first *meta*-photocyloaddition reaction was reported by Wilzbach and Kaplan and Bryce-Smith, Gilbert and Orger in 1966.[4] The *meta*-photocyloaddition reaction is a photochemically induced cycloadditon of an alkene across a benzene derivative, which gives rise to a complex tricyclic fused ring

system. The *meta*-photocycloaddition reaction between ethane and benzene can be represented in three different forms shown below (scheme 1.1).




**Scheme 1.1:** *meta*-photocycloaddition of benzene and ethane.

While the *meta*-photocycloaddition of benzene is very well documented in the literature and has been used many times in organic synthesis, the mechanism has still not been fully elucidated. Generally it is thought that the reaction proceeds *via* the excitation of the benzene ring to its first singlet state ($s_1$) by irradiation with 254 nm UV light which in turn forms an arene-alkene exciplex (scheme 1.2)

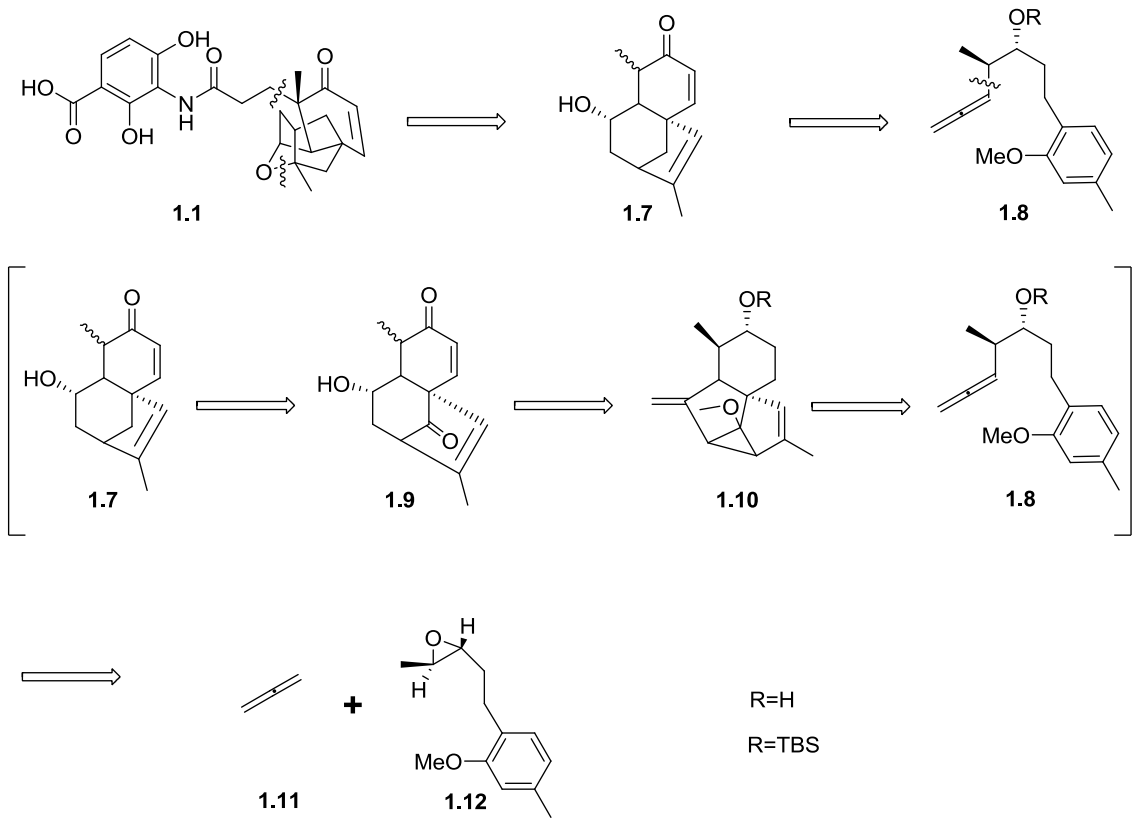



**Scheme 1.2:** General mechanism of *meta*-photocycloaddition.

During the *meta*-photocycloaddition as the reaction proceeds, the complex **1.3** is polarised with positive charge at position 1, with an allylically distributed negative charge between positions 3 and 5 when the allene undergoes 2,6-addition. As the alkene-arene bonds are formed a biradical intermediate **1.4** has been proposed in the formation of compounds **1.5** and **1.6** (scheme 1.2).

## 1.2. Retrosynthetic analysis for platensimycin 1.1.

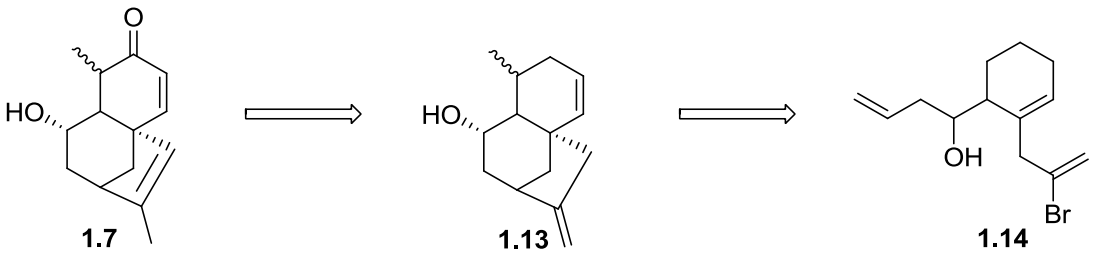
In the first approach to platensimycin **1.1** a *meta*-photocycloaddition reaction will be employed to secure the framework of the title compound. The retrosynthetic analysis for **1.1** is shown below (scheme 1.3).




**Scheme 1.3:** Retrosynthetic analysis for platensimycin **1.1**.

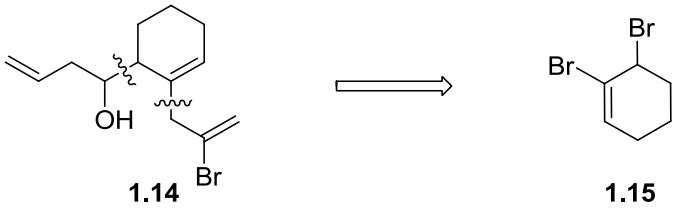
In the first approach the tricyclic compound **1.7** is synthesised by an intramolecular *meta*-photocycloaddition of aromatic compound **1.8** and try to form the tricyclic core of the platensimycin **1.1** using compound **1.7**. The synthesis of **1.7** from **1.8** is shown in a stepwise manner above (scheme 1.3). After the successful formation of the tricyclic core **1.7** we shall try to attach the aromatic ring to form the total synthesis of platensimycin **1.1**.

In another approach we shall synthesize the tricyclic core **1.7** of platensimycin **1.1** by using the retrosynthesis shown above (scheme 1.4).




**Scheme 1.4:** Retrosynthetic analysis for precursor **1.7**.

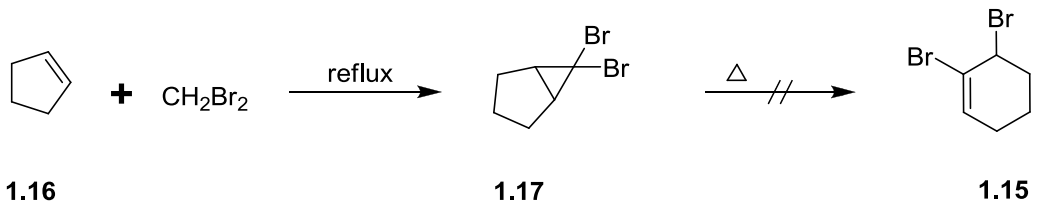
The aim is to synthesize **1.7** by the radical cyclisation of the triene **1.14.** The proposed retrosynthesis for the triene **1.14** by using 1,6-dibromo-cyclohexene **1.15** is seen below (scheme 1.5).




**Scheme 1.5:** Retrosynthesis for **1.14**

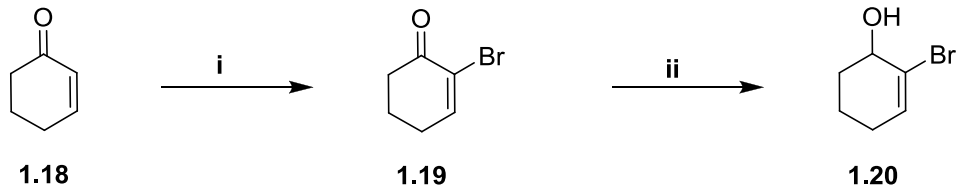
The molecule **1.15** was difficult to synthesize as it is an unstable compound and we were having very difficult time in isolating the compound. A rapid approach for the synthesis of **1.15** was done by utilising the procedure involved in the rearrangement of 6,6-dibromobicyclo[3.1.0]hexane[5] **1.17**.

### 1.3. Synthesis of 1,6-dibromo-cyclohexene 1.15.




**Scheme 1.6:** Synthesis of 1,6-dibromo cyclohexene **1.15**.

6,6-Dibromobicyclo[3.1.0]hexane **1.17** was obtained when the reaction product from cyclopentene **1.16** and dibromomethane was distilled rapidly at low temperature. A subsequent experiment showed that the 6,6-dibromide **1.17**, in the absence of solvent, undergoes isomerisation to the 1,6-dibromo-cyclohexene **1.15** when heated at 155 $^{o}$C for a short time (scheme 1.6). We could not isolate the compound even after several attempts. We could not get the compound even after high vaccum distillation. We abandoned this scheme and moved on to another method involving cyclohexenone **1.18** (scheme 1.7).

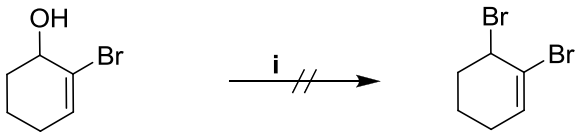



**1.18** **1.19** **1.20**

*Reagents and conditions:* i. $Br_2$, DCM, $Et_3N$, 0 $^{o}$C - rt, 3 h, 72%; ii. $CeCl_3 \cdot 7H_2O$/MeOH, $NaBH_4$, DCM, rt, 1 h, 80%;

**Scheme 1.7:** Synthesis of 2-bromo-cyclohex-2-enol **1.20**.

Cyclohexenone **1.18** was readily converted into 2-bromo-cyclohex-2-enone **1.19** by bromination using bromine in the presence of triethylamine. 2-Bromo-cyclohex-2-enone **1.19** was reduced to 2-bromo-cyclohex-2-enol **1.20** by utilizing $NaBH_4$ and cerium salt involving Luche's reduction[6,7] (scheme 1.7). An unsuccessful attempt to the formation of dibromide **1.15** from 2-bromo-cyclohex-2-enol **1.20** (scheme 1.8) can be seen below in table 1.1.



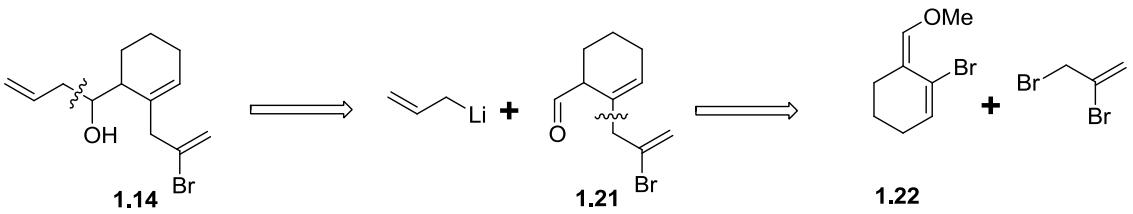

**1.20** **1.15**

**Scheme 1.8:** Bromination of **1.20**.

**Table 1.1**: Bromination of **1.20** under different reaction conditions.

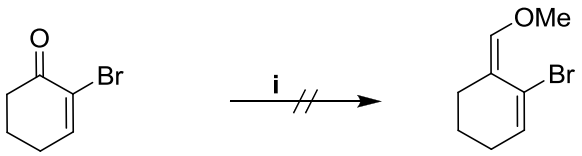
| S.No | Reactant | Reagents and Conditions (i) | Product 1.15 | Inference |
|---|---|---|---|---|
| 1 | **1.20** | $PBr_3$, HBr, DCM, rt, 7 h. | Nil | Starting material recovered. |
| 2 | **1.20** | $CF_3COOH$, $PBr_3$, HBr, DCM, rt, 12 h. | Nil | Starting material recovered. |
| 3 | **1.20** | $CF_3COOH$, Ag Salts, $PBr_3$, HBr, DCM, rt, 12 h. | Nil | Starting material recovered. |

### 1.4. Second approach for the synthesis of triene 1.14.




**Scheme 1.9:** Retrosynthesis of **1.14** using **1.22**.

After an unsuccessful attempt to convert the 2-bromo-cyclohex-2-enol **1.20** to 1,6-dibromo-cyclohexene **1.15** under various reaction conditions (scheme 1.8), we envisaged a new scheme for the synthesis of triene **1.14** utilising **1.22** (scheme 1.9). In the process of formation of diene **1.22** we unsuccessfully tried to utilise Wittig reaction conditions on bromocyclohexenone **1.19**. The compound **1.19** decomposed (scheme 1.10).

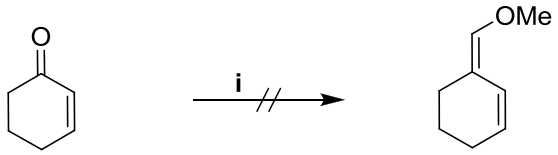



**1.19** **1.22**

*Reagents and conditions:* i. *n*-BuLi (2.5M), -78 $^{o}$C, $Ph_3P(CH_2MeO)Br$/THF;

**Scheme 1.10:** Wittig reaction on bromo-cyclohexenone **1.19**.

At this stage we attempted to use the same conditions used above (scheme 1.10) on cyclohexeneone **1.18**. We failed to obtain any desired results (scheme 1.11). The failure of Wittig reactions can be due to conjugated double bond with the carbonyl group in **1.19** and **1.18**. Usually the reaction would be successful if there is no conjugated double bond involved with the carbonyl group.



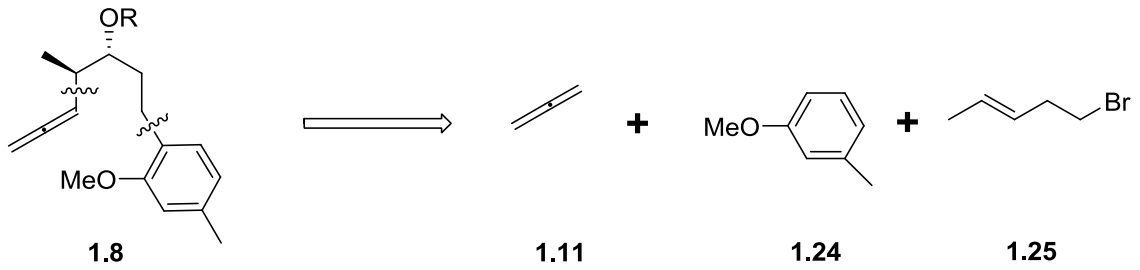

**1.18** **1.23**

*Reagents and conditions:* i. *n*-BuLi (2.5M), -78 $^{o}$C, $Ph_3P(CH_2MeO)Br$/THF;

**Scheme 1.11:** Wittig reaction on cyclohexenone **1.18**.

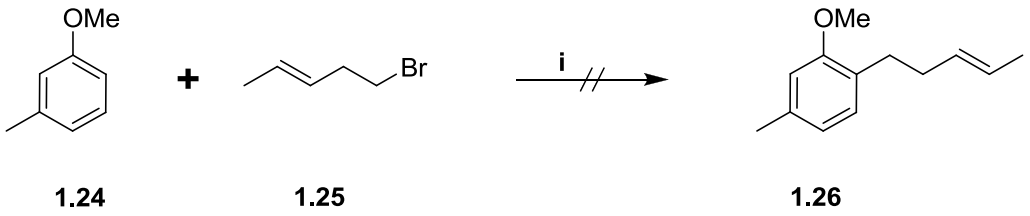
## 1.5. Photochemical approach for the total synthesis of platensimycin 1.1.

We envisaged a scheme wherein the aromatic compound **1.8** would undergo intramolecular *meta*-photocycloaddition to form the tricyclic core of the platensimycin **1.1**. The compound **1.8** could be obtained by utilising methyl anisole **1.24** (scheme 1.12).




**Scheme 1.12:** Retrosynthesis of **1.8**.

Methyl anisole **1.24** did not undergo otholithiation with **1.25**. The electrophilic aromatic substitution reaction failed to yield any desired result (scheme 1.13).

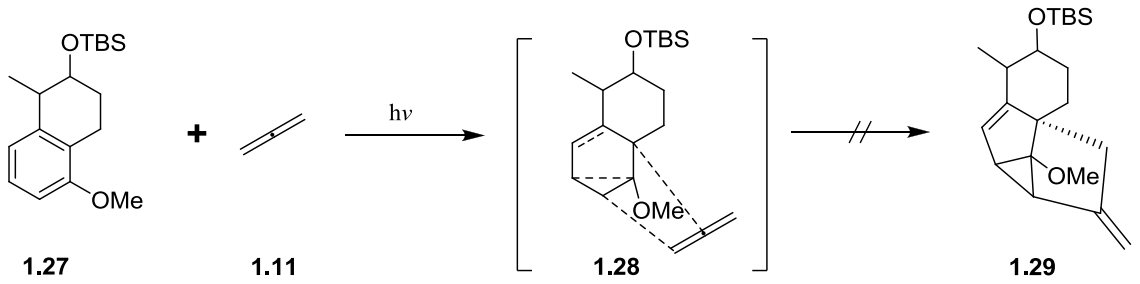



*Reagents and conditions:* i. *n*-BuLi (2.5M), -78 $^{o}$C, then **1.25**, THF, 6 h;

**Scheme 1.13:** Substitution reaction on methylanisole **1.24**.

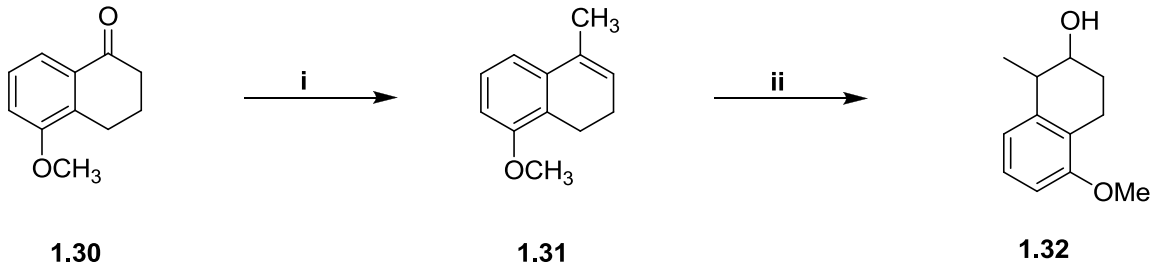
### 1.5.1. Synthesis of 1.27 and photochemistry using allene gas 1.11.

At this stage a rapid approach to platensimycin **1.1** was attempted by using tetralin/allene photochemistry (scheme 1.14). A novel photochemical approach to platensimycin **1.1** was obtained using trisubstituted decalin **1.27**. A *meta*-photocycloaddition[4] reaction between allene **1.11** and aromatic benzene ring of **1.27** would give the tetracyclic compound **1.29**. The reaction proceeds *via* the excitation of the benzene ring of **1.29** to its first singlet state ($s_1$) by irradiation with UV light which in turn forms an arene-alkene exciplex **1.28** (scheme 1.14) to give tetracyclic complex **1.29**.




**Scheme 1.14:** Photochemistry of **1.27** using allene gas **1.11**.

5-Methoxy tetralone **1.30** would undergo addition of methyl group through Grignard's reagent followed by elimination of water to give 8-methoxy methyl tetralin **1.31**. The compound **1.31** would undergo further hydroboration to give trisubsituted decalin **1.32** (scheme 1.15)**.** The structure of **1.32** was confirmed by X-ray crystallographic studies (figure 1.3).




*Reagents and conditions*: i. $CH_3MgBr$, THF, Δ, 1 h; ii. *p*-TSA/toluene, $H_2O$, 1 h; iii. $BH_3$·THF, NaOH, 35% $H_2O_2$, 74% (overall yield);

**Scheme 1.15:** Synthesis of **1.32**.

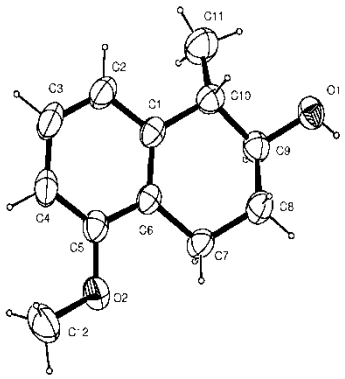
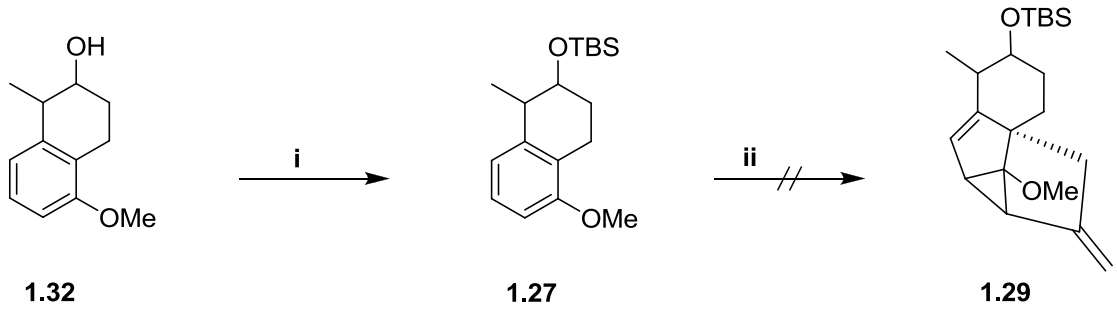



**Figure 1.3:** X-ray crystallographic structure of **1.32.**



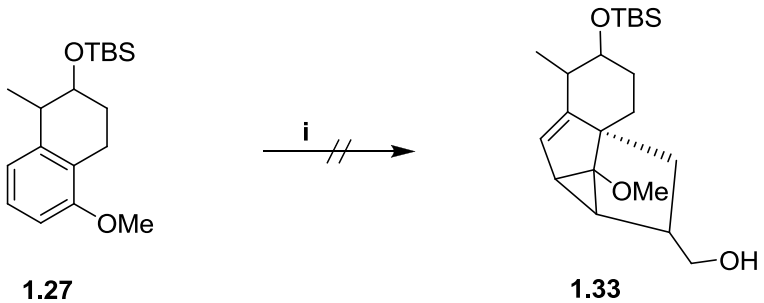

**1.32** **1.27** **1.29**

*Reagents and conditions*: i. TBSCl, Imidazole, DCM, 80%. ii. allene gas **1.11**, $CH_3CN$, *hv*(16w UV lamp);

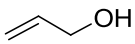
**Scheme 1.16:** Photochemistry **1.27** using allene gas.

The compound **1.32** undergoes OH protection using TBSCl to give **1.27** which was dissolved in $CH_3CN$. Allene gas **1.11** was dissolved in $CH_3CN$ and the gas was pumped using syringe from the allene gas **1.11** cylinder. The photochemical reaction was carried out using a 16w U.V lamp and the reaction mixture was subjected to photolysis (scheme 1.14). The photolysis was observed in 30 mins, 60 mins, and after that in 1 h intervals. There was no change in the aromatic structure of **1.27** and the starting material was recovered. Though some peaks were observed but they might be due to allene gas photochemical reactions. As we failed to obtain any desired results (scheme 1.16) we now intended to use allyl alcohol, which was replaced with $CH_3CN$ as solvent (scheme 1.17).

### 1.5.2. Photochemistry of 1.27 using allyl alcohol.




**1.27** **1.33**

*Reagents and conditions*: i.  , *hv*(125w UV lamp);

**Scheme 1.17:** Photochemistry of **1.27** using allyl alcohol.

We tried to use allyl alcohol instead of allene gas **1.11** as allyl alcohol can be used as a solvent. The compound **1.27** was dissolved in 20 mL of allyl alcohol and a 125w U.V lamp was used as a light source. We changed the light source as in previous reaction with allene gas (scheme 1.16) with 16w U.V lamp, the reaction failed to give any desired result. The mixture was subjected to photolysis (scheme 1.17). The reaction was monitored at 15 mins, 30 mins, 1 h, 2 h, 3 h and 5 h duration. The starting material completely reacted after 5 h. The compound was semi-solid viscous material and it was partially dissolvable in DCM and was not dissolvable in ether and ethyl acetate. The yield was very low and we could not get the desired compound **1.33**. The $H^1$-NMR showed the loss of aromatic character of the starting material and subsequently we failed to analyse the structure of the resulting product.

We stopped working on the total synthesis of platensimycin **1.1** at this stage and moved on to another project, which is the total synthesis of kainic acid **2.1**.

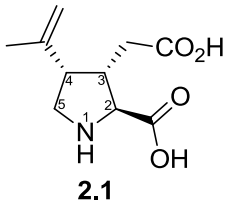
# CHAPTER TWO

# 2. Introduction

# 2.1. Introduction to Kainoids

### 2.1.1. Structure and Isolation

α-(−)-Kainic acid **2.1** (figure 2.1) is the parent compound which consists of a pyrrolidine ring with stereo centers at the C-2, C-3 and C-4 positions, all with the *S* configurations. The simplest derivative of kainic acid **2.1** is allokainic acid **2.2** whose only structural difference is at the C-4 position where it possesses the opposite *R* stereochemistry.



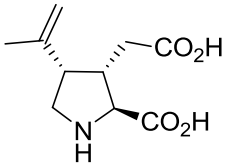
**2.1**

**Figure 2.1:** Kainic acid **2.1**.

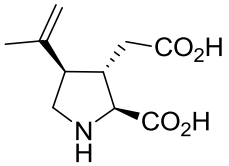
Kainoid amino acids are an important class of pyrrolidine dicarboxylic acids, structurally derived from kainic acid **2.1**. Structural and configurational differences are found in the C-4 substituent and give rise to a series of kainoid amino acids as shown in figure 2.2[8].

α-(−)-Kainic acid **2.1** is considered as the parent compound, as it was the first to be isolated in 1953 from the Japanese marine algae called ‘‘Kainin-sou’’ or ‘‘Makuri’’ (*Digenea simplex*)[9] along with its C-4 epimer allokainic acid **2.2**. Since then, kainic acid **2.1** has been found in other organisms such as the algae *Centrocerus calvulatum*[10] and the Corsican moss *Alsidium helminthocorton*.[11,12]

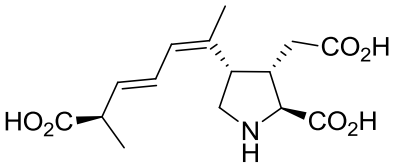
Originally the structure was assigned as 3-carboxymethyl-4-isopropenylpyrrolidine-2-carboxylic acid in a series of classical chemical degradations and syntheses of degradative products by Japanese chemists in 1955.[13-15] Marimoto was the first, to assign the relative stereochemistry by chemical studies,[16] and this has been supported by X-ray analysis.[17,18]



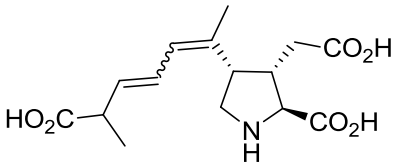
α-(–)-Kainic acid **2.1**



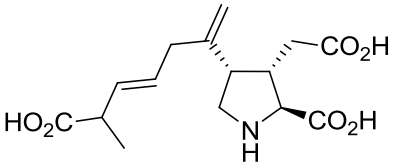
α-(+) –Allokainic acid **2.2**



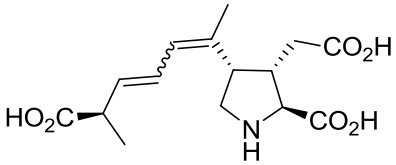
(–)-Domoic acid **2.3**



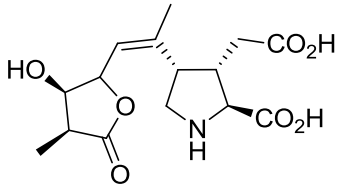
Isodomoic acid A (*Z*, *E*) **2.4**
Isodomoic acid B (*E*, *E*) **2.5**



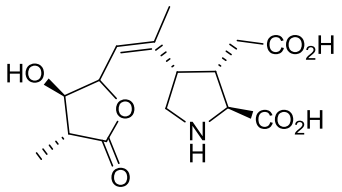
Isodomoic acid C **2.6**



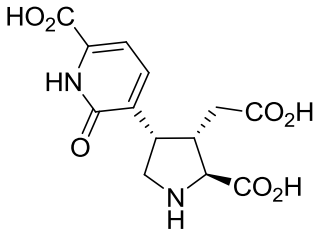
Isodomoic acid D (*Z*, *Z*) **2.7**
Isodomoic acid E (*E*, *E*) **2.8**
Isodomoic acid F (*E*, *Z*) **2.9**



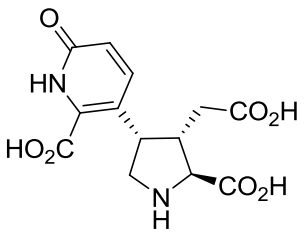
Domoilactone A **2.10**



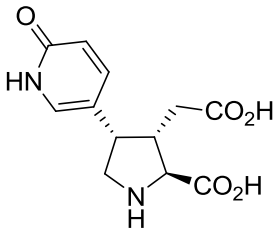
Domoilactone B **2.11**



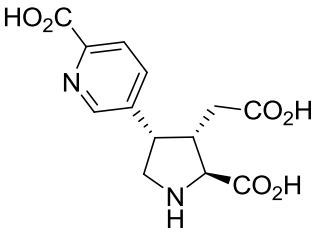
Acromelic acid A **2.12**



Acromelic acid B **2.13**



Acromelic acid C **2.14**



Acromelic acid D **2.15**

**Figure 2.2:** The kainoid amino acid family.[8]

### 2.1.2 Biological Properties

Kainoid amino acids exhibit an array of biological properties, including anthelmintic,[17,18] epileptogenic,[19] insecticidal[20] and neuroexcitatory activity.[21,22] Among the kainates, kainic acid **2.1** exhibits an exceptional pharmacological profile, especially acting as an antiworming agent[20]. Recently, it has also been widely applied in neuroscience research as a neurodegenerative agent for modeling epilepsy[23,24], Alzheimer's disease[25], and Parkinson's disease.[26]

Kainic acid **2.1** (*Digenea simplex*), has been used for its anthelmintic (anti-intestinal worm) properties for more than a thousand years.[27] These properties are highly dependent on the relative configuration of the stereocenters, with the *cis* stereo-chemistry at the C-3 and C-4 substituents appearing to be crucial to the anthelmintic function of all known stereoisomers. Since then, kainic acid **2.1**, has been found to have an intense anthelmintic effect, about 10 times that of santonin.[17,18] As such the C-4 epimer allokainic acid **2.2** has been found to have only a weak anthelmintic effect.[28]

The insecticidal properties of kainoids have long been utilised by the population of Yakushima Island, Japan. They used the extract of red algae *Chondria armata*, from which kainic acid **2.1** and domoic acid **2.3** have since been isolated, for its fly killing properties. Since then these compounds have shown to be potent insecticides towards the cockroach.[29] The insecticidal activity is attributed to the nature of the side chain at the C-4 position of the pyrrolidine ring.[20]

The predicated neuroexcitatory properties of the kainoid excitatory amino acids as conformationally restricted glutamic acid analogues have been well investigated.[30-33] The kainoids have a strong and selective affinity towards the kainite receptors, and have been shown to selectively block neuronal processes and are considerably valuable as tools in neurological studies. Their extremely potent activity, in both the vertebrate and invertebrate glutamergic systems,[34] have been shown to be related to many neurodegenerative diseases.

The pharmacological effects and patterns of neuronal degeneration,[34] observed after injection of kainates have been shown to mimic the symptoms similar to those observed in patients suffering from neuronal diseases such as Huntington's chorea[35] and

Epilepsy.[23] Thus kainates have been used as tools in experimental models for central nervous system disorders, such as senile dementia.[30-33] Although kainoids are very unlikely to become part of the treatment for neuronal diseases, as their extremely potent activity in both the invertebrate and vertebrate glutamergic system, leads to specific neuronal death in the brain.[34] The information obtained from the biological models could provide new solutions in the treatment for neuronal diseases.

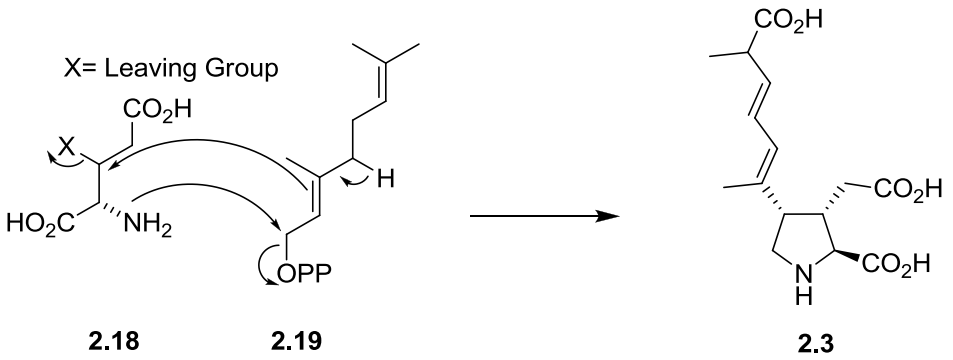
After studying the biological properties of the many kainoids, the neuroexcitatory activity has been shown to be strongly attributed to the nature of the C-4 substituent. A double bond is essential to giving good excitatory activity and is also dependent upon the bonds conformation.[36-38] For example in CPAA **2.16** (figure 2.3), which has no C-4 substituent, shows no kainite-type selectivity. As previously mentioned the *cis*-relationship between C-3 and C-4 appendages, plays a key role in excitatory activity. Kainic acid **2.1** shows enhanced activity compared to the C-4 epimer allokainic acid **2.2**. Similarly, dihydrokainic acid **2.17** (figure 2.3),[37] which has no π-electrons within its C-4 substituent, exhibits no excitatory acitivity. The nature of the side chain at the C-4 postion of the pyrrolidine ring also plays a crucial role in enhanced insecticidal activity.[20] Compared to isodomoic acid C **2.6**, domoic acid **2.3** is 23 times more active against the American cockroach.[29]


**2.16** **2.17**

**Figure 2.3:** CPAA **2.16** and dihydrokainic acid **2.17**.

### 2.1.3 Biosynthesis:

Wright suggested a biosynthetic pathway for domoic acid **2.3** and this route was likely to be a general pathway to all kainoids.[39] The proline ring structure was generated by condensation of an activated glutamate derivative with an isoprenoid chain. Although both glutamic acid derivative **2.18** and geranyl pyrophosphate **2.19** are two different biogenetic units, both are entirely derived from acetate. Labelling experiments with [1-$^{13}$C] acetate and [1,2-$^{13}$C] acetate were used to provide evidence for condensation between glutamic acid **2.18** and a geranyl pyrophosphate **2.19** (scheme 2.1). Similarly, the biosynthetic pathway for kainic acid **2.1** was suggested by Wright, in which the proline ring system is generated by condensation of isopentenyl pyrophosphate (as an isoprenoid unit).[39]



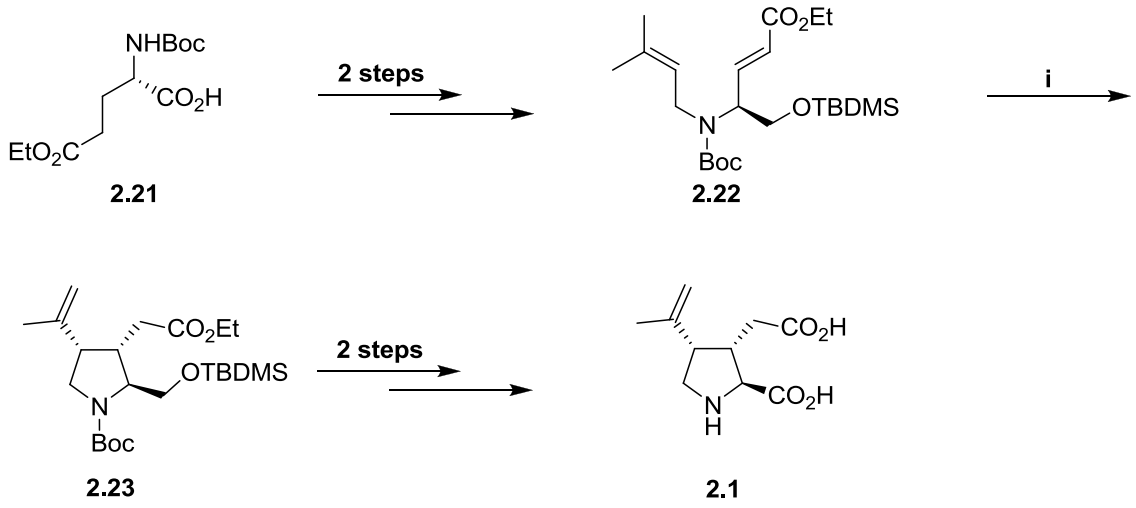

**Scheme 2.1:** Biosynthesis of domoic acid **2.3**.

### 2.1.4. Previous Syntheses:

To date, more than forty total syntheses and synthetic approaches to kainic acid **2.1** have been reported. The challenging *cis*-3,4 stereochemistry of kainoids, except for allokainic acid **2.2**, have led to the development of several synthetic strategies. Further, the total synthesis of kainic acid **2.1**, has been a synthetic challenge due to the three contiguous stereogenic centers in the pyrrolidine ring. As the biological acitivity of kainic acid is linked to the *trans* C-2/C-3 and *cis* C-3/C-4 stereochemistry, any synthesis needs to have efficient control of this relative stereochemistry. As such most of the syntheses to date start with enantiomerically pure starting material, for example, serine or glutamic acid.

#### 2.1.4.1. Oppolzer's Synthesis[40]

The first enantioselective total synthesis of kainic acid **2.1** was completed by Wolfgang Oppolzer and Klaus Thirring in 1982.[40] They used the commercially available (*S*)-glutamic acid as the starting material.



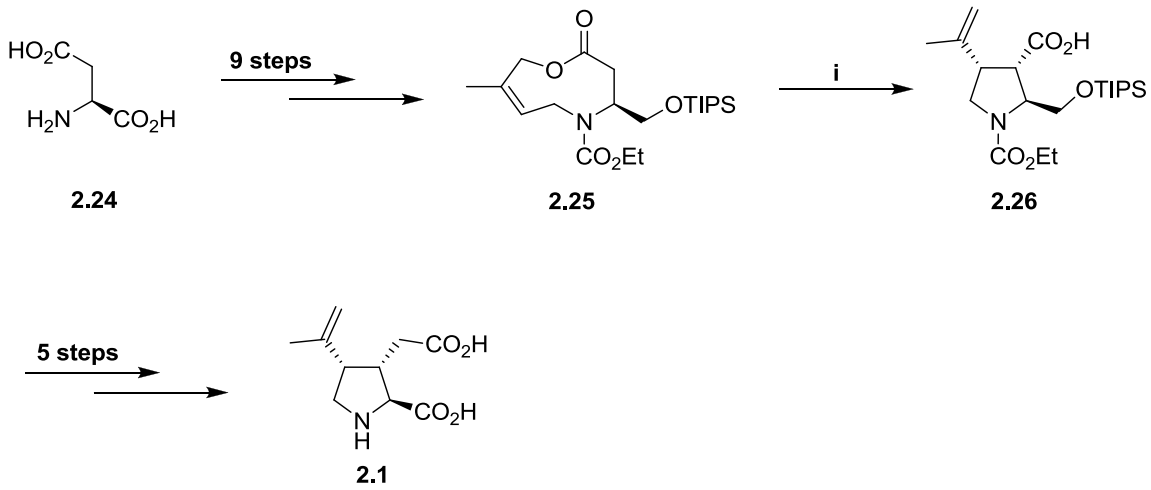

*Reagents and conditions*: i. Toluene, 130 $^{o}$C, (75%);

**Scheme 2.2:** Oppolzer's synthesis of kainic acid **2.1**.

The acid group was protected and the alkene was attached to the amido group by a reduction-oxidation sequence (scheme 2.2). The *α,β*-unsaturated ester was formed by successive selenation of the enolate, oxidation, and selenoxide elimination. This 1,6 diene **2.22** underwent an ene- reaction in toluene at 130 $^{o}$C to give the required *cis* C-3/C-4 stereochemistry **2.23**. Further deprotection gave rise to kainic acid **2.1**. This was the first and shortest total synthesis of kainic acid **2.1** comprising only 6 steps with an overall yield of 5%.

### 2.1.4.2. Knight's Synthesis[41]

An enantiospecific route of kainic acid **2.1** was developed by Knight and co-workers in 1987 using a stereocontrolled Ireland-Claisen rearrangement of a suitable azalactone **2.25**, to construct kainic acid's **2.1** C-3/C-4 bond.[40]




**2.24** **2.25** **2.26** **2.1**

*Reagents and conditions*: i. (a) LDA, TBSCl, THF, -100 $^{o}$C – 20 $^{o}$C. (b) $K_2CO_3$, MeOH/$H_2O$ (55% over 2 steps);

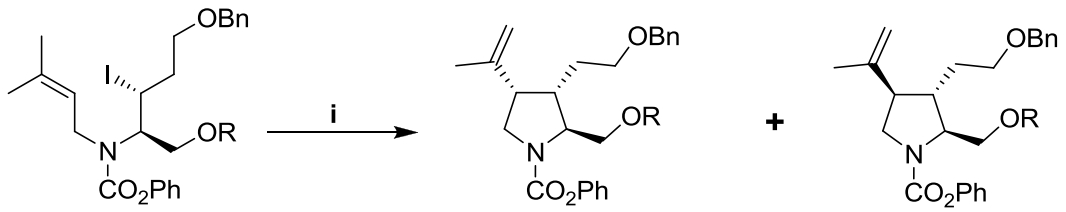
**Scheme 2.3:** Knight's synthesis of kainic acid **2.1**.

Azalactone **2.25** was formed by utilising the starting material L-aspartic acid **2.24**. Here, the actual rearrangement occurred as the reaction mixture was warmed to ambient temperature. Hydrolysis of the resulting silyl ester gave the desired

pyrrolidinecarboxylic acid **2.26** in 2 steps (scheme 2.3). Arndt-Eistert homologation of the acid **2.26** followed by oxidation furnished kainic acid **2.1**.

### 2.1.4.3. Baldwin's Synthesis[42]

Baldwin and Li reported the application of a homolysis and *β*-elimination sequence to the enantioselective synthesis of kainic acid **2.1** and allokainic acid **2.2** in the year 1987. They reported two methods, one of which pertains to the cyclisation of the iodide **2.28** (scheme 2.4). The key iodide **2.28** was obtained in 54% yield from L-threonine methyl ester in four steps[35]. The cobaloxime mediated cyclisation of **2.28** afforded a mixture of the separable isomers **2.29** and **2.30** with the *syn*-pyrrolidine **2.29** predominating (5:3). These isomers on deprotection and oxidation gave kainic acid **2.1** and allokainic acid **2.2** respectively. The Co(I), in addition to the formation of pyrrolidine ring, introduces a double bond at the C-4 side chain *via* a dehydrocobaltation process.[43]




**2.28** **2.29** **2.30**

R= $^{t}$BuMe$_2$Si

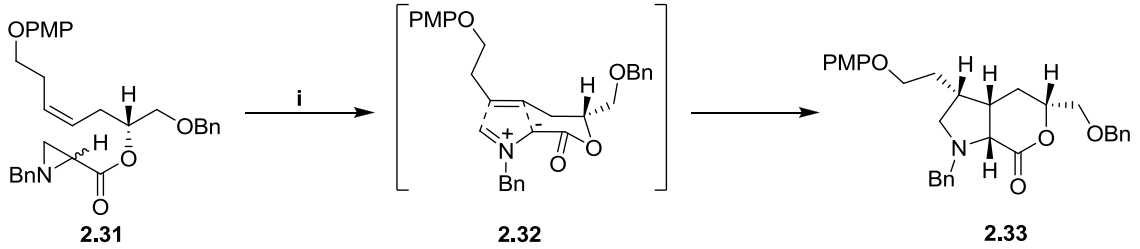
*Reagents and conditions*: i. Cobaloxime(I);

**Scheme 2.4:** Baldwin's synthesis of kainic acid **2.1** and allokainic acid **2.2**.

### 2.1.4.4. Takano's Synthesis

Takano's interest in kainic acid **2.1** has been well documented, with four enantioselective syntheses to his credit.[44,48,50,51] The first synthesis reported in 1988 involved an intramolecular 1,3-dipolar cyclisation of aziridine ester **2.31**. Thermolysis of ester **2.31** in xylene and diastereoselective intramolecular cycloaddition gave the

pyrrolidine lactone **2.33** in all-*cis* configuration (scheme 2.5).[44] The stereochemical outcome was explained by the author as a result of the ylide adopting *exo*-conformation **2.32** for the active intermediate in which the bulky benzyloxymethyl group assumes an equatorial orientation with respect to the forming $\delta$-lactone moiety. Hydrolysis of the lactone moiety **2.33** followed by sequential oxidative treatment ($CrO_3$ and $HIO_4$) introduced the C-3 and C-4 appendages in kainic acid **2.1**. The ester at the C-2 position required further epimerisation to afford the required kainic acid **2.1**.

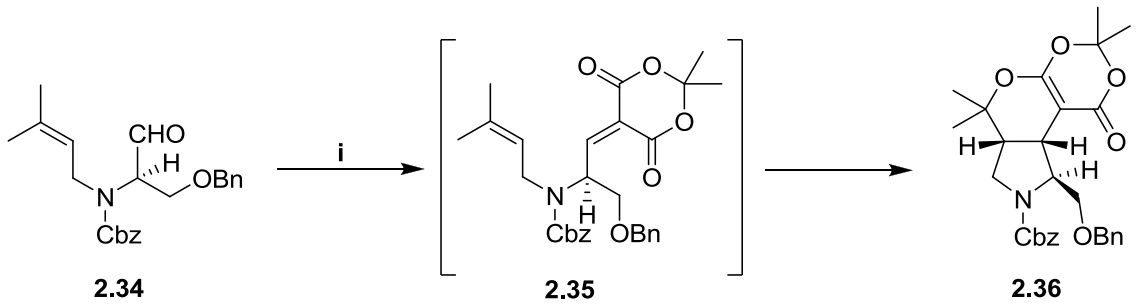



**2.31** **2.32** **2.33**

*Reagents and conditions*: i. xylene, 305-310 $^{o}$C, sealed tube (70%);

**Scheme 2.5:** Takano's synthesis of kainic acid **2.1**.

In the same year 1988, Takano[45] proposed another enantioselective synthesis of kainic acid **2.1** using an intramolecular-hetero Diels-Alder reaction to construct the *cis*-C-3/C-4 ring junction of kainic acid **2.1**. The diene **2.35**, formed on reaction of **2.34** with Meldrum's acid,[46] accompanied by intramolecular [4+2] cycloaddition to give **2.36** as a single diastereomer shown below (scheme 1.6). The stereochemical outcome was presumed to be a result of the $sp^2$-planar like configuration of the carbamate nitrogen, which allows efficient [4π + 2π] overlap of only the *endo*-conformer. The subsequent opening of lactone **2.36** generated a suitable precursor for the formation of kainic acid **2.1**(scheme 2.6).



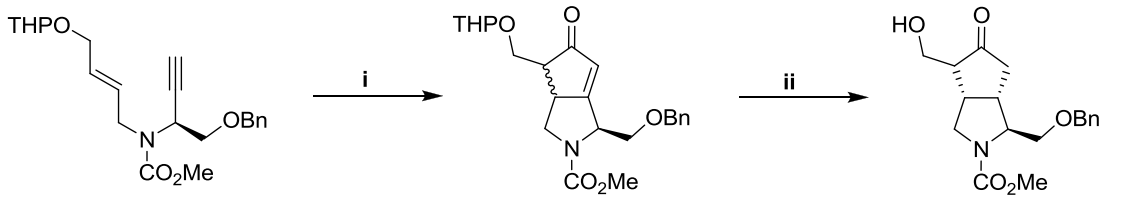

**2.34** **2.35** **2.36**

*Reagents and conditions*: i. Meldrum's acid, EDTA;

**Scheme 2.6:** Takano's synthesis of kainic acid **2.1**.

The overall yield of kainic acid **2.1** from the precursor obtained from lactone **2.36** was 22%.

Another new enantiospecific route to kainic acid **2.1** *via* the intramolecular Pauson-Khand reaction was proposed by Takano (scheme 2.7) in the year 1992.[47] The treatment of **2.37** with $Co_2(CO)_8$ and then NMO, furnished a bicyclic enone **2.38** as an inseparable mixture of diastereoisomers in 85% yield. The mixture further undergoes a stereoselective reduction of the alkene and removal of the THP group, to furnish the desired adduct **2.39**, as major product in 60% yield. The adduct **2.39** undergoes further modifications in 9 steps to give kainic acid **2.1**.




**2.37** **2.38** **2.39**

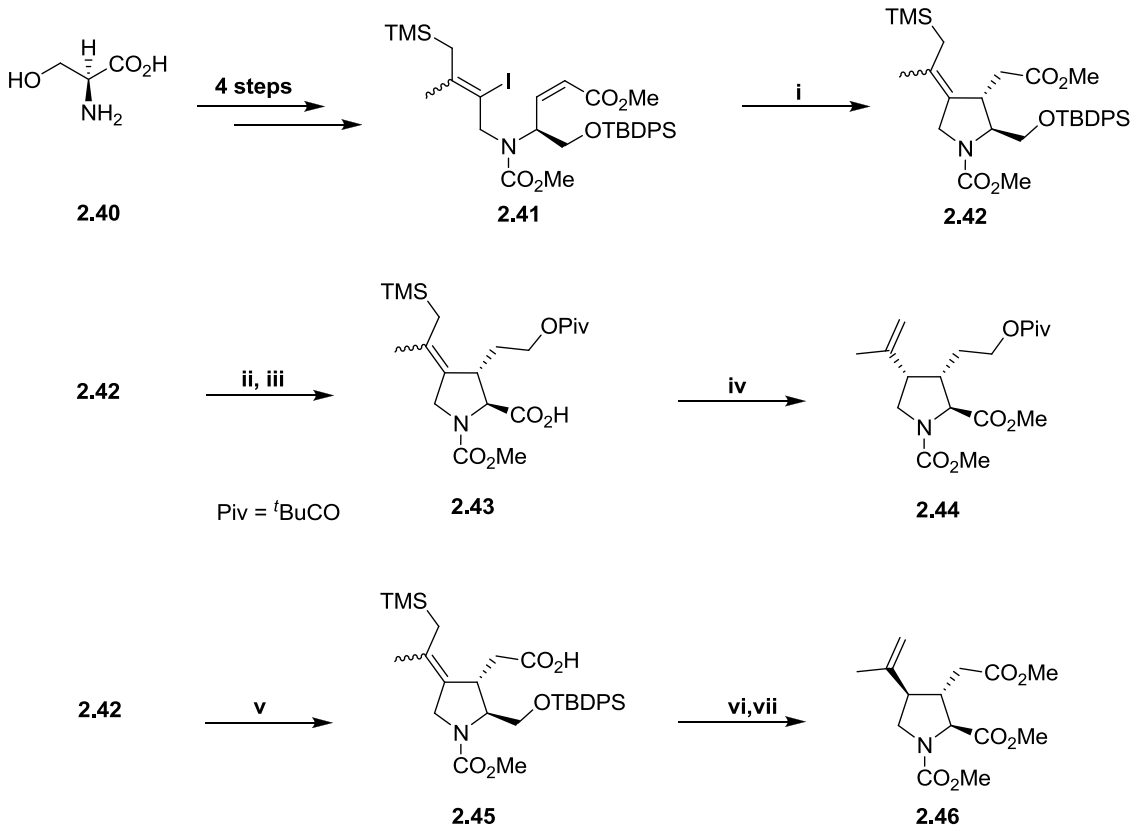
(60 %, major product)

*Reagents and conditions*: i. (a) $Co_2(CO)_8$ (1.2 eq.), benzene, rt. (b) NMO (6 eq.), DCM, 0 $^oC$ (85% over 2 steps); ii. (a) $LiAlH_4$, CuI, HMPA-THF (1:4), -78 $^oC$ (b) *p*-TSA, MeOH, rt, then separation by $SiO_2$ column;

**Scheme 2.7:** Takano's synthesis of kainic acid **2.1**.

Takano, starting from L-Serine **2.40** proposed another novel asymmetric synthesis of kainic acid **2.1** and allokainic acid **2.2** using protodesilylation step[48] in the year 1993.

*α,β*-Unsaturated ester **2.41** was prepared in four steps starting from L-Serine **2.40**. Treatment of **2.41** with tributyltin hydride in the presence of catalytic amount of AIBN in boiling benzene resulted in a highly diastereoselective radical cyclisation to give exclusively the substituted pyrrolidine **2.42**. The compound **2.42** was found to be a useful intermediate and underwent crucial protodesilylation step using various substrates which were prepared from **2.42**. Pyrrolidine **2.42** undergoes further modifications to give compounds **2.43** and **2.45** (scheme 2.8). Two-step oxidation of the primary alcohol of **2.43**, followed by $BF_3{\cdot}Et_2O$-mediated protodesilylation proceeded with opposite diastereoselectivity to give the 3,4-*cis*-pyrrolidine **2.44**, which on further treatment in two steps gave kainic acid **2.1**. Treatment of **2.45** with $BF_3{\cdot}Et_2O$ in methylene chloride, directed an intramolecular protodesilylation with complete diastereoselectivity to give 3,4-*trans*-pyrrolidine **2.46**. The compound **2.46** in another 2 steps gives allokainic acid **2.2**.

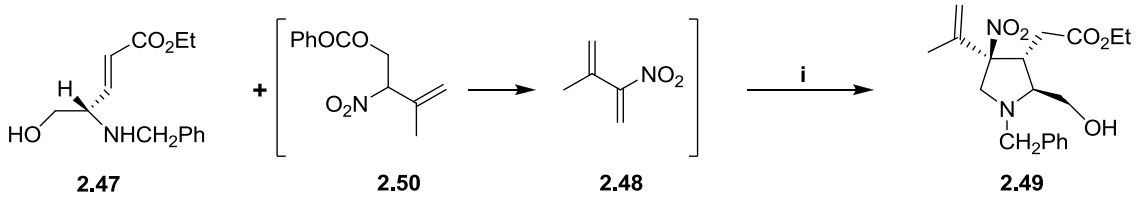



*Reagents and conditions*: i. $Bu_3SnH$, AIBN (catyalyst), benzene, reflux; ii. (a) DIBAL, DCM, -78 $^oC$. (b) $^tBuCOCl$, $Et_3N$, DMAP, DCM. (c) 46% HF, MeCN; iii. (a) $(COCl)_2$, DMSO, DCM, -60 $^oC$ then $Et_3N$. (b) $NaClO_2$, $NaHPO_4$, 2-methylbut-2-ene, $^tBuOH$-$H_2O$ (4:1); iv. (a) 10 eq. $BF_3{\cdot}Et_2O$, DCM. (b) $CH_2N_2$, $Et_2O$; v. 5% KOH in MeOH; vi. (a) 3 eq. $BF_3{\cdot}Et_2O$, DCM. (b) $CH_2N_2$, $Et_2O$. (c) 46% HF, MeCN; vii. (a) $H_2CrO_4$, acetone. (b) $CH_2N_2$, $Et_2O$;

**Scheme 2.8:** Takano's synthesis of kainic acid **2.1** and allokainic acid **2.2**.

### 2.1.4.5. Spalluto's Synthesis[49]

Based on a one-pot tandem Michael reaction methodology, Spalluto and co-workers in 1992 envisaged a new enantioselective route to the kainoid family (scheme 2.9). The pyrrolidine **2.49** which could give the desired kainic acid **2.1** was obtained by simply stirring equimolar quantities of **2.47** and **2.48** at room temperature in ethanol for 15 h. The electrophilic component **2.48** was obtained from **2.50** *in situ*, where **2.47** acts both as donor-acceptor partner as well as basic catalyst for generating **2.48**. Here nitro group plays a noteworthy role in crucial stereo- and regio-chemical control.



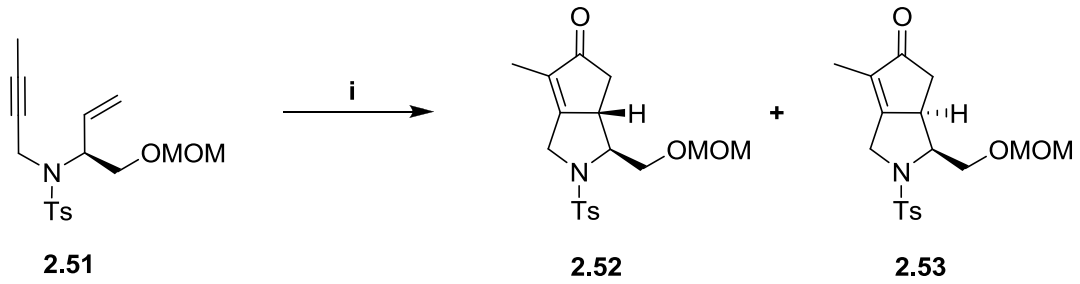

**2.47** **2.50** **2.48** **2.49**

*Reagents and conditions*: i. Ethanol, rt, 15 h;

**Scheme 2.9:** Spalluto's synthesis of kainic acid **2.1**.

### 2.1.4.6. Yoo's Synthesis[50,51]

Another synthetic route for kainic acid **2.1** has been developed based on the Pauson-Khand reaction as the key step, was developed by Yoo[50] in 1993. The optically active vinylacetylene **2.51** was subjected to Pauson-Khand conditions which yielded the *trans*-bicyclic enone as an inseparable mixture of diastereomers (**2.52 + 2.53**) in 95% yield (scheme 2.10). The diastereomer **2.52** underwent further modifications and was then converted to kainic acid **2.1** in overall 5 steps.

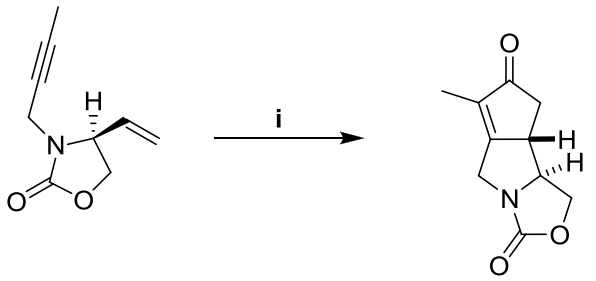



**2.51** **2.52** **2.53**

*Reagents and conditions*: i. (a) $Co_2(CO)_8$, DCM. (b) TMANO (95% over 2 steps, (**2.52**: **2.53**) = (1.7:1));

**Scheme 2.10:** Yoo's synthesis of kainic acid **2.1**.

The precursor **2.51** used in the Pauson-Khand reaction (scheme 2.10) was further modified by Yoo[51] in 1994, to increase the diastereoselectivity by employing a rigid oxazolidinone moiety **2.54**. Under the similar conditions (scheme 2.10), the oxazolidinone **2.54** gave a single isomer **2.55** in 93% yield (scheme 2.11).

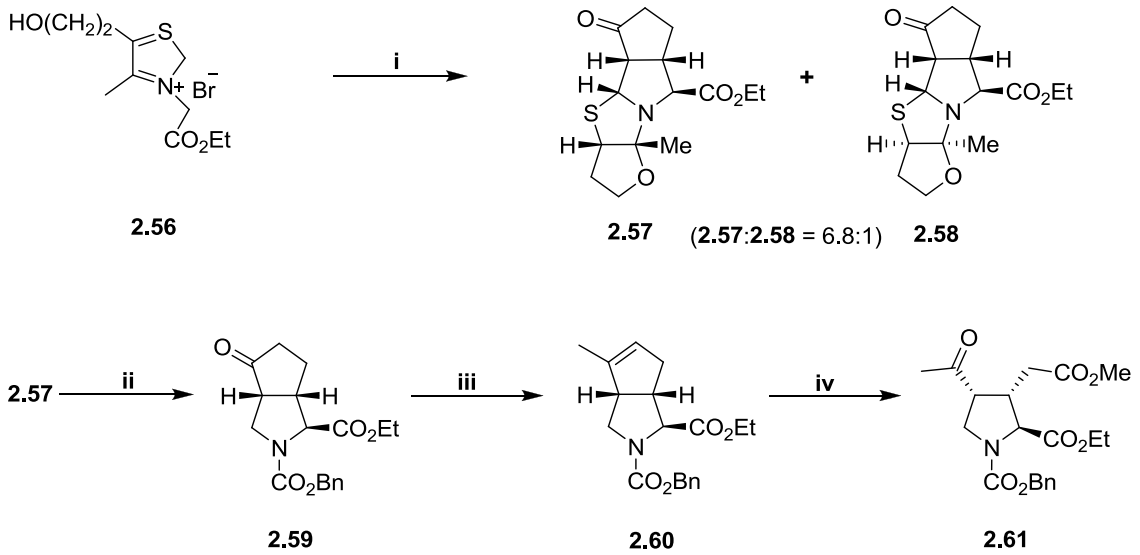



**54** **55**

*Reagents and conditions*: i. $Co_2(CO)_8$, DCM; ii. TMANO (93% over 2 steps);

**Scheme 2.11:** Yoo's synthesis of kainic acid **2.1**.

### 2.1.4.7. Monn's Synthesis[52]



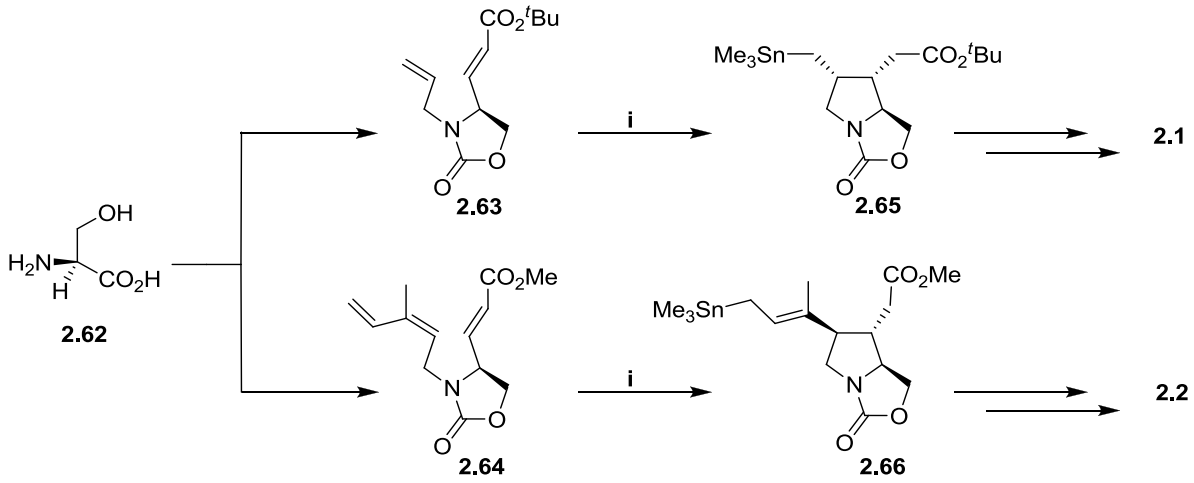

*Reagents and conditions*: i. 2-cyclopentenone, $Et_3N$, $CH_3CN$, rt; ii. (a) $Bu_3SnH$, AIBN, toluene, reflux. (b) HCl, $H_2O$, rt. (c) Benzylchloroformate, NaOH, 5 $^oC$, 64%; iii. (a) MeLi, $TiCl_4$, DCM, $Et_2O$. (b) $BF_3$-$Et_2O$, DCM, reflux; iv. $RuO_2$, $NaIO_4$, $CCl_4$, $CH_3CN$, $H_2O$, rt;

**Scheme 2.12:** Monn's synthesis of kainic acid **2.1**.

A stereocontrolled thiazolium ylide approach to kainic acid **2.1** was reported by Monn and Valli in 1994. They successfully prepared a separable mixture of tetracycles **2.57** and **2.58** on a large scale (up to 1.5 mol) in excellent (70-80%) isolated yields (scheme 2.12). Reductive cleavage of the thiazoline C-S bond with $Bu_3SnH$ followed by *in situ* hydrolysis of the resulting hemiaminal followed by protection of nitrogen as its benzyl carbamate afforded **2.59** in 64% yield. In further two steps they could successfully afford the formation of **2.61** which led to the formation of kainic acid **2.1** in 8% overall yield from 2-cyclopentenone.[52]

### 2.1.4.8. Hanessian's Synthesis[53]

A trimethylstannyl-mediated radical carboxylization approach was proposed by Hanessian in 1996 for the stereoselective synthesis of kainic acid **2.1** and allokainic acid **2.2**. The synthesis commenced with L-serine **2.62**, which was transformed into compound **2.63** and **2.64** in 6 steps for each compound (scheme 2.13).

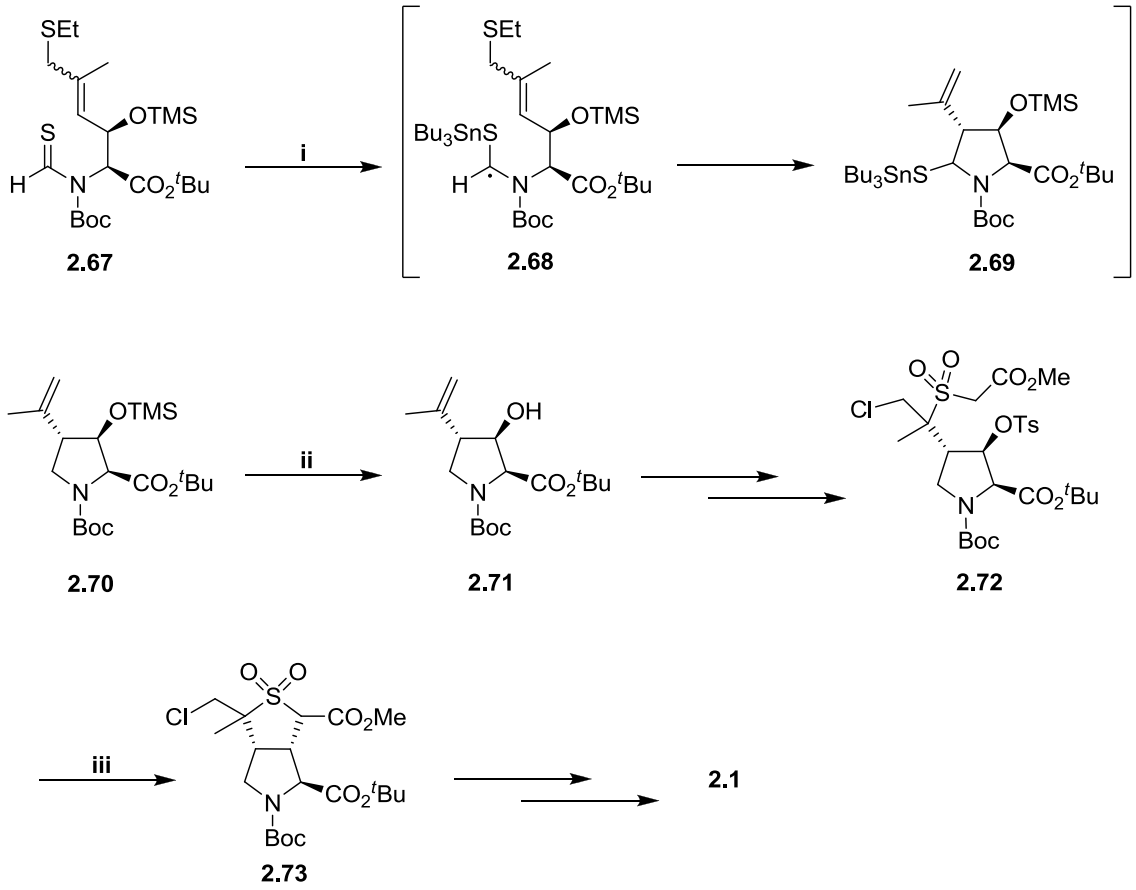



*Reagents and conditions*: i. $Me_3SnCl$, slow addn. of $NaCNBH_3$, $^tBuOH$, reflux, AIBN;

**Scheme 2.13:** Hanessian's synthesis of kainic acid **2.1** and allokainic acid **2.2**.

The diene **2.63** was treated with trimethyltin hydride generated under Stork's conditions[54]; a mixture of stannylated compounds was obtained, favouring the *cis* stereochemistry at the C3-C4 centers in a ratio of 2.8:1. However, a slow addition of sodium cyanoborohydride over a period of 1h to a refluxing solution containing the compound **2.63** and trimethyltin chloride afforded the cyclised product **2.65** and its C4 isomer as an inseparable mixture in 88% yield without compromising the *cis/trans* ratio. The mixture was then treated with CAN in methanol to oxidatively cleave the C-Sn bond in order to obtain the destannylation of **2.65**. The resultant dialkyl acetal[53] formed was further transformed into kainic acid **2.1** 10 steps in 2% overall yields. Under the similar conditions, substrate **2.66** was converted into allokainic acid **2.2** in 3% overall yield**.**

### 2.1.4.9 Bachi's Synthesis[55]



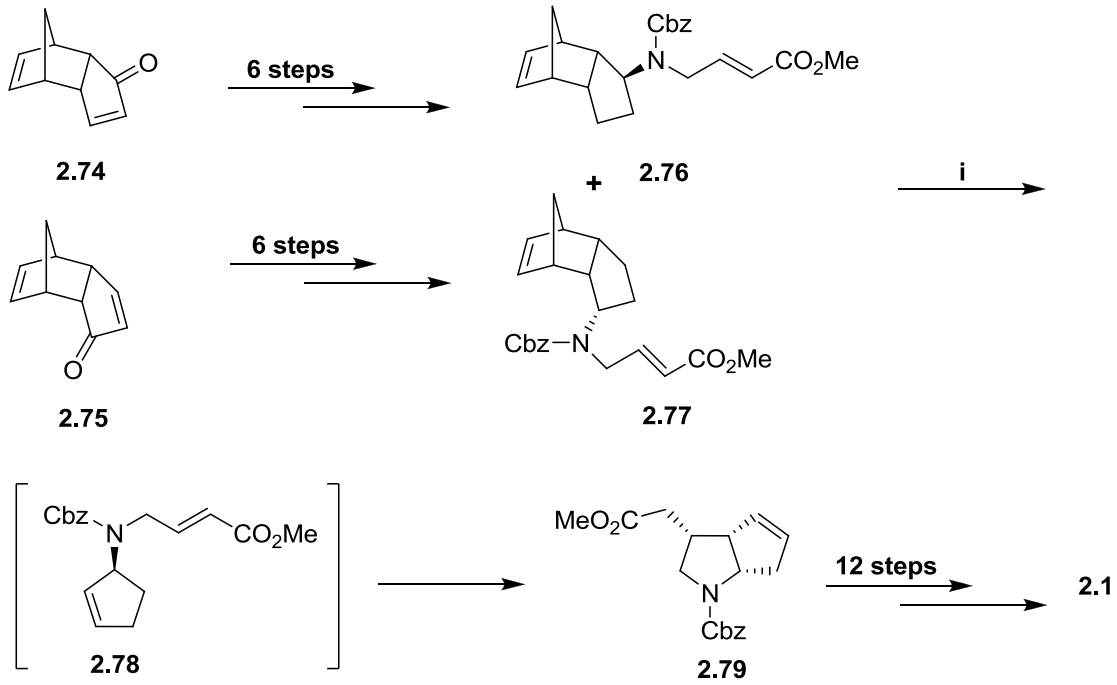

*Reagents and conditions*: i. EtSH, AIBN, toluene, 60 $^{o}$C, 5 h; ii. MeOK, THF/MeOH/methyl formate (40:2:1), rt, 3 h, neutralized with AcOH; iii. MeOK and methyl formate in MeOH/THF;

**Scheme 2.14:** Bachi's synthesis of kainic acid **2.1**.

The stereocontrolled synthesis of kainic acid **2.1** by sulfur radical mediated cyclisation was reported by Mario D. Bachi in 1997. The highly functionalised monothioformimide **2.67** was formed in three steps.[55] The radical cyclisation of **2.67**, mediated by *n*-$Bu_3SnH$/AIBN gave the tetrasubstituted pyrrolidine **2.70**, which on desilylation gave the enantiomerically pure key compound **2.71**, in 73% overall yield starting from **2.67**. The compound **2.71** was converted to the rather stable sulfone **2.72** in further two steps (scheme 2.14). Treatment of the sulfone-tethered acetic acid ester **2.72** with potassium methoxide and methyl formate in MeOH/THF gave the desired cyclic $\alpha$-chloromethyl-sulfone **2.73**. The compound **2.70** upon further treatment gave kainic acid **2.1**.

### 2.1.4.10. Ogasawara's Synthesis

An intramolecular ene-reaction was utilised in the synthesis of kainic acid **2.1** by Kunio Ogasawara[56] in the year 1997.

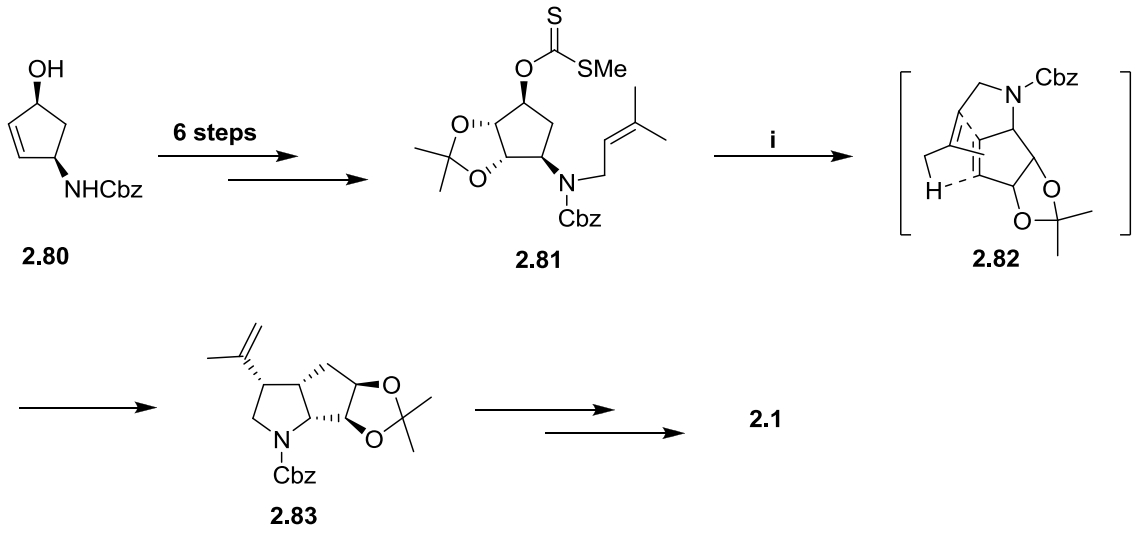



*Reagents and conditions*: i. PhOPh, reflux, 60 min, 90% (>99% ee);

**Scheme 2.15:** Ogasawara's synthesis of kainic acid **2.1**.

The compounds **2.76** and **2.77** were formed starting from the enantiomers of optically pure ketodicyclopentadiene **2.74** and **2.75**. These underwent a concurrent one-pot retro-Diels Alder reaction and intramolecular ene reaction of the transient 1,6 diene **2.78**, to afford an all-*cis* bicyclo product **2.79** in 90% yield and >99% ee (scheme 2.15). The bicyclic pyrrolidine **2.79** gave the core to the total synthesis of kainic acid **2.1**.

Another route proposed by Ogasawara in the year 2000 involved a concurrent Chugaev *syn*-elimination[57] and intramolecular ene reaction as the key step in the synthesis of kainic acid **2.1** (scheme 2.16).



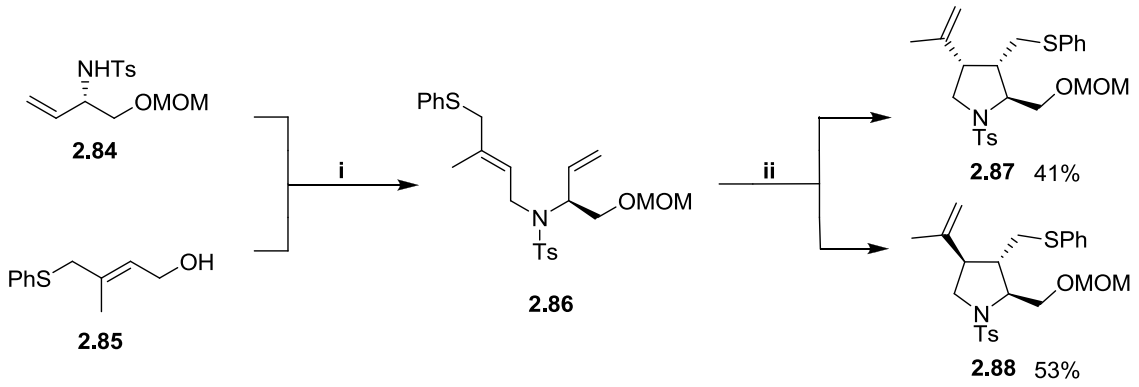

*Reagents and conditions*: i. $NaHCO_3$, PhOPh, reflux, 45 min, (72%);

**Scheme 2.16:** Ogasawara's synthesis of kainic acid **2.1**.

The key xanthate ester **2.81** was prepared from the enantiopure starting material *cis*-4-carbobenzoxyamino-2-cyclopentenol **2.80** in 6 steps. Thermolysis of xanthate ester **2.81** in diphenyl ether in the presence of sodium hydrogen carbonate gave the tricyclic product **2.83**, bearing the trisubstituted pyrrolidine framework required for the kainic acid **2.1** in 72% yield as a single diastereomer. This was formed, presumably, via the transient *exo*-1,6-diene intermediate **2.82**.

### 2.1.4.11. Naito's Synthesis[58]

Takeaki Naito in the year 1997, proposed an enantioselective synthesis of kainic acid **2.1** via a route involving a sulfur radical addition-cyclisation-elimination reaction (scheme 2.17). The requisite diene **2.86** was prepared through a Mitsunobu reaction of the (*S*)-vinylglycinol **2.84** with the hydroxyl sulphide **2.85**. The sulfur radical addition-cyclisation-elimination reaction of **2.86**, in the presence of thiophenol and AIBN in boiling benzene under nitrogen gave the 3,4-*cis*-(**2.87**) and 3,4-*trans*-(**2.88**) in 41 and 53% yields respectively. The resulting carbon radical undergoes 5-*exo*-*trig* cyclisation[53]. The isomers **2.87** and **2.88** were potential synthetic compounds for the total synthesis of kainic acid **2.1** and allokainic acid **2.2** respectively.

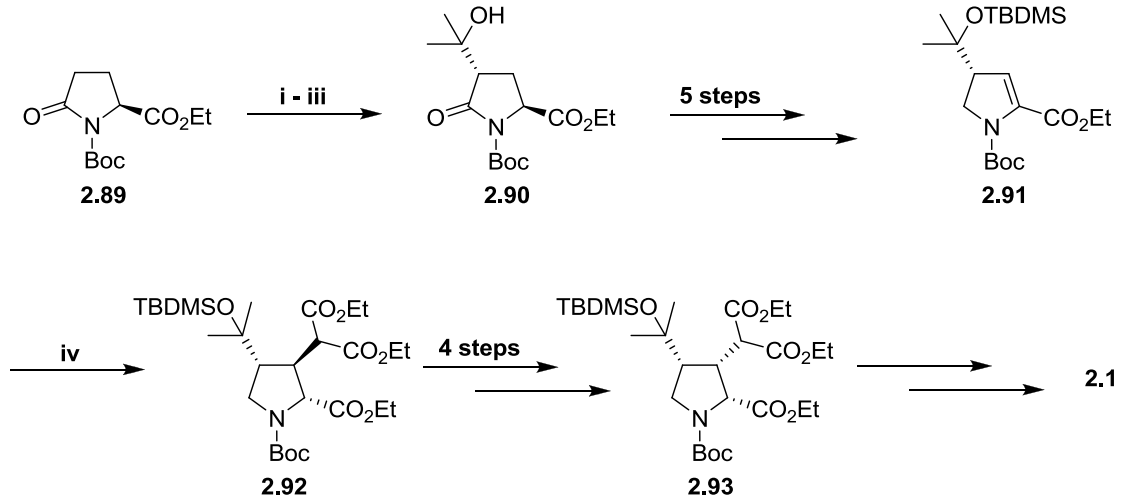



*Reagents and conditions*: i. DEAD, $Ph_3P$, 68%, ii. PhSH, AIBN, $C_6H_6$;

**Scheme 2.17:** Naito's synthesis of kainic acid **2.1** and allokainic acid **2.2**.

### 2.1.4.12. Rubio's Synthesis[59]

Rubio in the year 1998 developed an approach to the synthesis of kainic acid **2.1** based on the stereocontrolled functionalization of *N*-Boc protected pyroglutamate ester **2.89** (scheme 2.18). $BF_3{\cdot}OEt_2$ mediated aldol condensation of the pyroglutamate lactam enolate using LiHMDS in acetone at -78 $^oC$ generated a mixture of *cis* and *trans* aldols (1:4 ratio), which were inseparable. To obtain the *trans* aldol **2.90**, it was necessary for the deprotection of the nitrogen. Subsequent reprotection of nitrogen under standard conditions gave **2.90** in 45% yield as a single isomer. **2.90** underwent reduction of ketone group, followed by generation of double bond to give Michael acceptor **2.91** in two steps. The addition of diethyl malonate anion to **2.91** furnished the Michael adduct **2.92** in 65% yield as a single diastereomer. Change of the stereochemistry at the C-3 position was achieved by the formation of double bond and subsequent hydrogenation of the double bond using $PtO_2$ in ethanol, which gave an all-*cis* prolinate **2.93** in two steps.[59] This was followed by decarboxylation, epimerization of the C-2 centre and deprotection finally gave kainic acid **2.1** in another 10 steps.

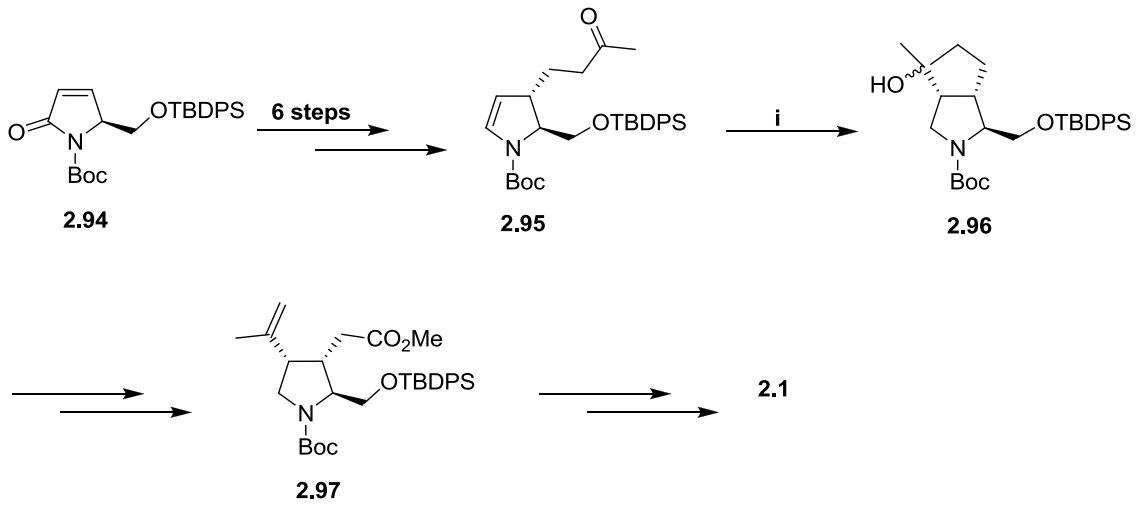



*Reagents and conditions*: i. LiHMDS/Acetone, $Et_2OBF_3$; ii. TFA/DCM, Separation; iii. $(Boc)_2O$/DMAP, (45% over 3 steps); iv. NaH/THF, $CH_2(CO_2Et)_2$ , 65%;

**Scheme 2.18:** Rubio's synthesis of kainic acid **2.1**.

### 2.1.4.13. Cossy's Synthesis[60]

Cossy's approach to the *cis*-C-3/C-4 geometry of kainic acid **2.1** in the year 1999 was accomplished by using a ketyl radical cyclisation on an ene carbamate (scheme 2.19).




*Reagents and conditions*: i. $SmI_2$, HMPA, $^t$BuOH, THF, (55%);

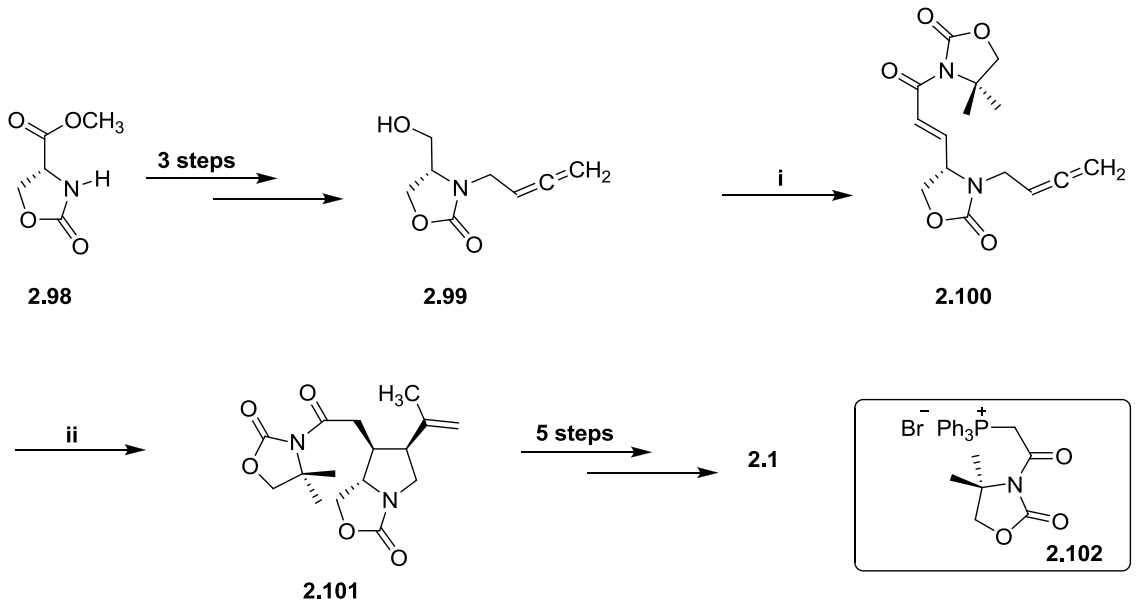
**Scheme 2.19:** Cossy's synthesis of kainic acid **2.1**.

Ketone **2.95** was synthesised from the enone **2.94** in 6 steps. This compound underwent a 5-*exo*-trig radical cyclisation using $SmI_2$, which gave the bicyclic pyrrolidine alcohol

**2.96** in 55% yield. The pyrrolidine alcohol **2.96** underwent dehydration, followed by oxidative cleavage and reduction to give alkene **2.97**, having the core structure of kainic acid **2.1**, which was subsequently converted to **2.1** in 4 steps.

### 2.1.4.14. Montgomery's Synthesis[61]

In the year 1999, Montgomery carried out a short and efficient total synthesis of kainic acid **2.1** and formal synthesis of allokainic acid **2.2**, using a highly stereoselective approach, involving complementary allene and alkyne cyclisations.



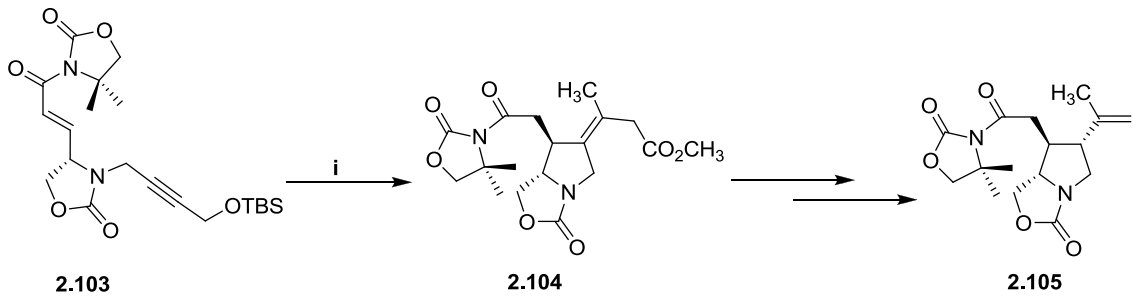

*Reagents and conditions*: i. (a) $(COCl)_2$, DMSO, $Et_3N$, DCM, -78 $^oC$. (b) **2.102**, DMAP, DCM, -20 – 25 $^oC$, 62%, 2 steps; ii. MeLi/$ZnCl_2$, $Ni(COD)_2$ (10 mol%), Ti(O $^i$pr)$_4$, 57% (98:2 diastereomeric ratio);

**Scheme 2.20:** Montgomery's synthesis of kainic acid **2.1**.

Oxazolidinone **2.98** was *N*-propargylated with propargyl bromide followed by homologation to afford allene **2.99**, which in turn was subjected to Swern oxidation[62] followed by Wittig olefination with a triphenyl phosphonium ylide **2.102** gave the cyclization substrate **2.100**. The substrate **2.100** was treated with MeLi/$ZnCl_2$ in the presence of $Ni(COD)_2$ and Ti(O $^i$pr)$_4$ directly afforded the cyclised compound **2.101** in a

57% yield with diastereomeric ratio 98:2 favouring the stereochemistry found in kainic acid **2.1** (scheme 2.20).

In the approach to a formal synthesis of allokainic acid **2.2**, D-serine methyl ester was efficiently converted to the cyclisation substrate **2.103**. This was followed by cyclisation of **2.103** with commercial trimethylaluminum and $Ni(COD)_2$ (10 mol %) in THF afforded a 73% yield of **2.104** with a favourable desired trans stereochemistry (scheme 2.21). The compound **2.104** was further reduced to afford **2.105** which could give the required allokainic acid **2.2**.

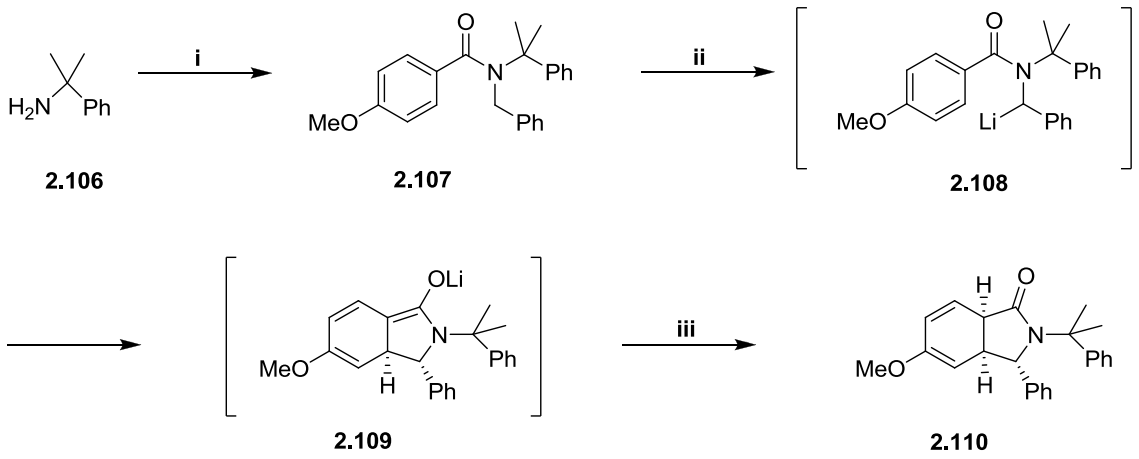



*Reagents and conditions*: i. (a) $AlMe_3$ (3 eq), 10 mol % $Ni(COD)_2$, THF, 0 $^oC$, 40 min, 73% (97:3 diastereoisomeric ratio). (b) HF·Pyr, THF, 0 $^oC$– 25 $^oC$, 24 h, 86%; then methylchloroformate (3 eq), pyridine, DCM, 0 $^oC$ - 25 $^oC$, 3 h, 83%;

**Scheme 2.21:** Montgomery's synthesis of allokainic acid **2.2**.

### 2.1.4.15. Clayden's Synthesis[63]

Clayden in the year 2000 described the dearomatising cyclisation of a lithiated *N*-benzyl *p*-anisamide in the synthesis of kainic acid **2.1**. The cyclisation substrate **2.107** was prepared starting from acylation of cumylamine **2.106** with *p*-anisoyl chloride **2.111**, followed by benzylation of the secondary amine. Amide **2.107** when lithiated with $^t$BuLi in the presence of HMPA, formed the cyclisation product **2.109**, which on protonation gave the dienyl ether **2.110** in good yield as a single regioisomer. Here we can see the introduction of three asymmetric centres in one synthetic operation from compound **2.108** (scheme 2.22).

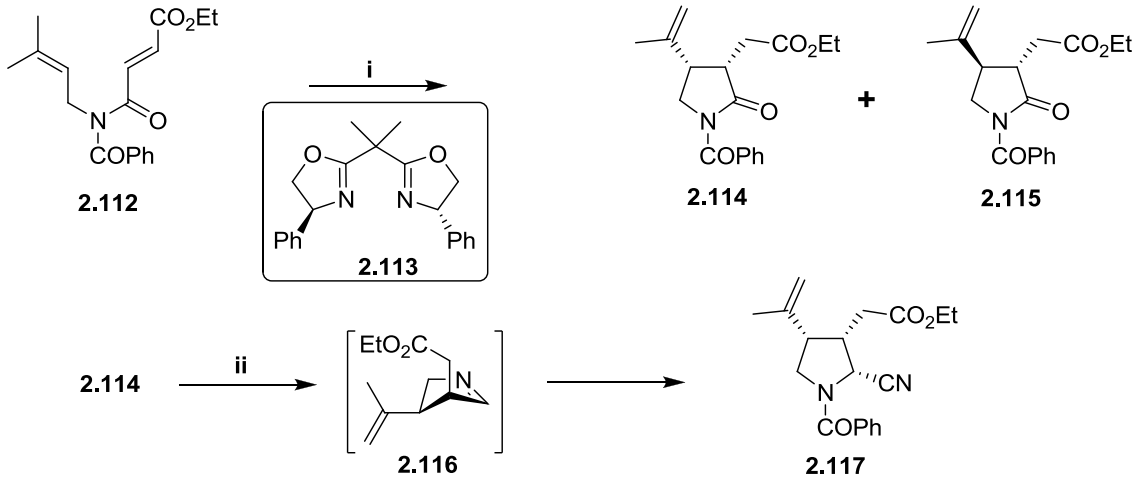



*Reagents and conditions*: i. (a) *p*-anisoyl chloride (**2.111**), $Et_3N$, DCM, (b) NaH, DMF, BnBr, 18 h, 82%; ii. $^tBuLi$ (2 eq.), HMPA (12 eq.), THF, -40 $^oC$, 60 h; iii. $NH_4Cl$;

**Scheme 2.22:** Clayden's synthesis of kainic acid **2.1**.

### 2.1.4.16. Ganem's Syntheses[64]

Ganem produced short and efficient total syntheses of kainic acid **2.1** in 2001, using an enantioselective, metal-promoted ene cyclisation.

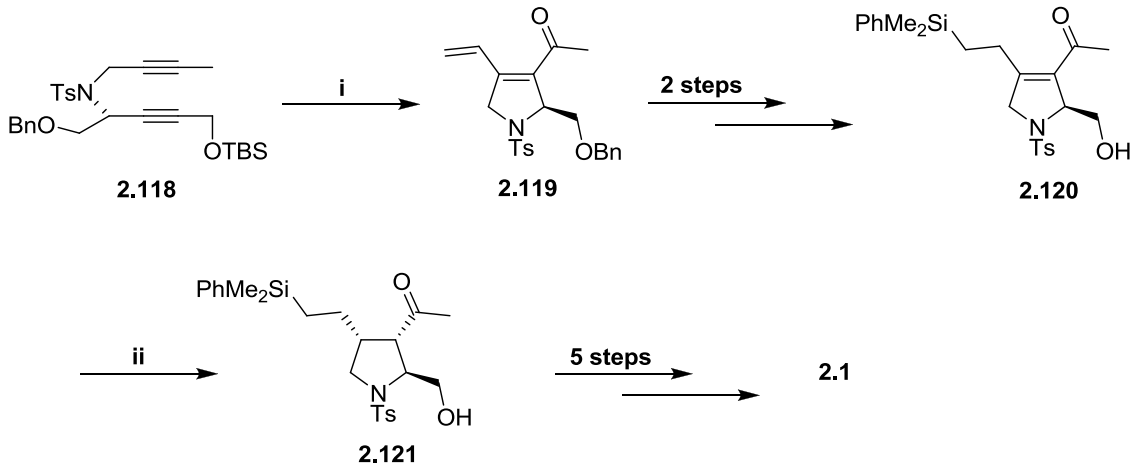



*Reagents and conditions*: i. (**2.113**), $Mg(ClO_4)_2$, DCM (72%), (**2.114**: **2.115**) = (>20:1); ii. a) $Cp_2ZrHCl$, THF, b) TMSCN, DCM (75% over 2 steps);

**Scheme 2.23:** Ganem's synthesis of kainic acid **2.1**.

The diene **2.112** was cyclised in the presence of $Mg(ClO_4)_2$ to generate the desired *cis*-isomer **2.114** predominantly. This high diastereoselectivity was attributed to the ligand **2.113**. Lactam **2.114** on reaction with Schwartz's reagent ($Cp_2ZrHCl$, 1.5 equiv in THF) generated an intermediate imine **2.116**, which was treated with cyanotrimethylsilane (TMSCN) in DCM to afford an all-*cis* nitrile **2.117** (scheme 2.23). The nitrile **2.117** underwent hydrolysis of both the ester and the nitrile groups, followed by epimerization of the C-2 substituent to give kainic acid **2.1** in a good overall yield of 20%.

### 2.1.4.17. Trost's Syntheses[65]



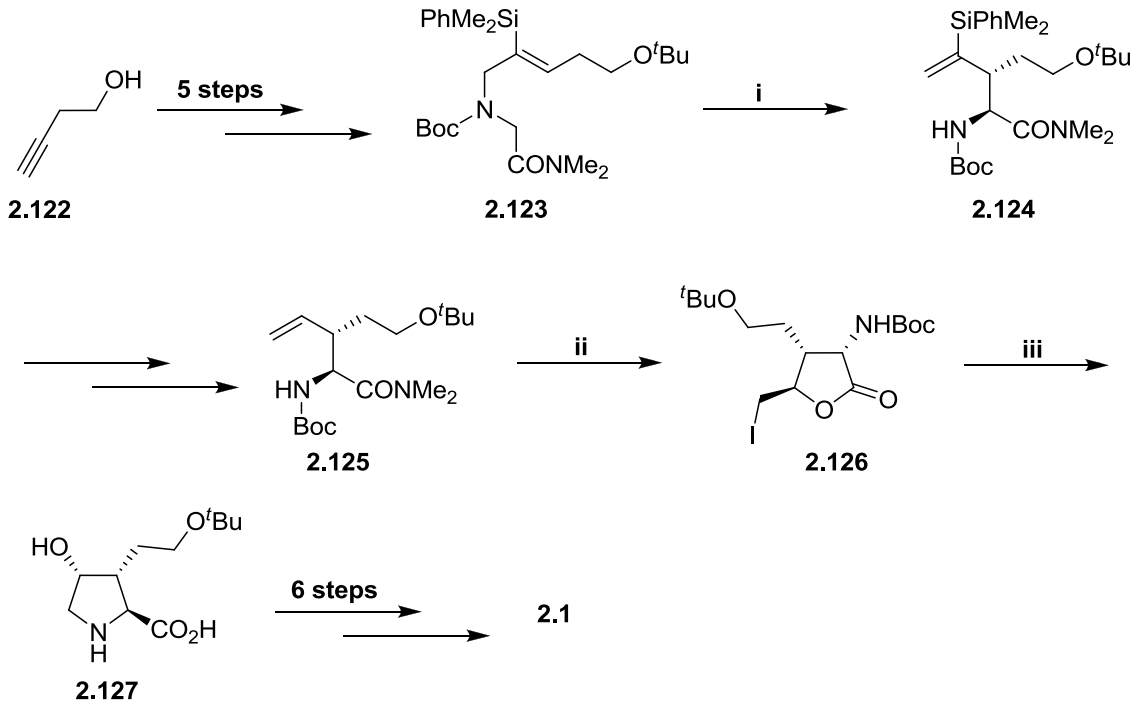

*Reagents and conditions*: i. 10%$[CpRu(CH_3CN)_3]PF_6$, 2% $H_2O$/acetone, 40 $^oC$, malonic acid (1 eq.), 3 h, 80% yield, 96% ee; ii. 20% $[Ir(cod)Py(PCy_3)]PF_6$, $H_2$ (2000 psi );

**Scheme 2.24:** Trost's synthesis of kainic acid **2.1**.

A novel route for the asymmetric total syntheses of kainic acid 2.1 was reported by the Trost group, where the key concept derived from a ruthenium-catalysed cycloisomerisation of a tethered alkyne-propargyl alcohol **2.118** to form a cyclic 3-acyl-4-vinyl pyrrolidine **2.119**. Silicon moiety was introduced by a novel 1,6 addition on compound **2.119** followed by olefin isomerisation and removal of benzyl group to form alcohol **2.120**. The stereochemistry of **2.121** was attained by the asymmetric reduction occurred with Crabtree's catalyst[66] $[Ir(cod)Py(PCy_3)]PF_6$ on alcohol **2.120**. Reduction of

ketone followed by oxidation of C-2 and C-3 groups of **2.121** would give kainic acid **2.1** in 4 subsequent steps.

### 2.1.4.18. Anderson's Synthesis[67]




*Reagents and conditions* i. LDA, 78%; ii. $I_2$, 85%; iii. TFA, KOH, 86%;

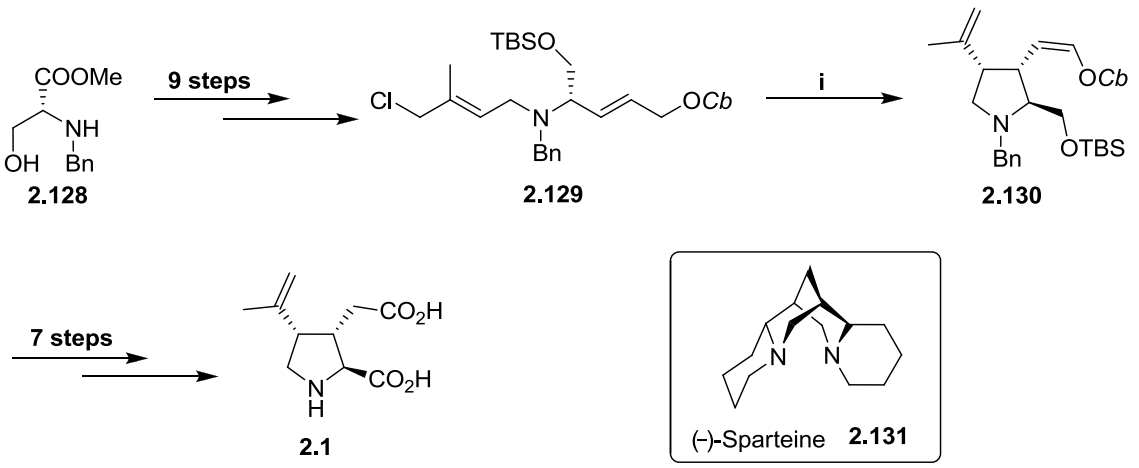
**Scheme 2.25:** Anderson's synthesis of kainic acid **2.1**.

Anderson's key stereochemical determining step in the route to the kainoid skeleton was an aza-[2,3]-Wittig sigmatropic rearrangement (scheme 2.25). Compound **2.123** was prepared from the commercially available 3-butyne-1-ol **2.122**. The aza-[2,3]-Wittig rearrangement was induced using LDA to give the unnatural amino acid derivative **2.124** in a 78% yield. This underwent protodesilylation to form **2.125.** Iodolactonization of **2.125** with $I_2$ in DME/$H_2O$ gave **2.126** as the major diastereoisomer. Deprotection of the amine and subsequent base-induced ring opening of the lactone followed by a 5-*exo*-tet cyclisation gave the proline skeleton **2.127** seen in kainic acid **2.1**. The synthesis was

completed in a further six steps to give the kainic acid **2.1** in overall 18 steps starting from 3-butyne-1-ol **2.122**.

### 2.1.4.19. Hoppe's Synthesis[68]

In the year 2004, Hoppe reported an enantioselective synthesis of kainic acid **2.1**, based on a (–)-sparteine **2.131** mediated asymmetric deprotonation of an intermediate carbamate **2.129**. *N*-benzyl-protected D-serine methyl ester hydrochloride **2.128** is converted to the key precursor carbamate **2.**129.[62]



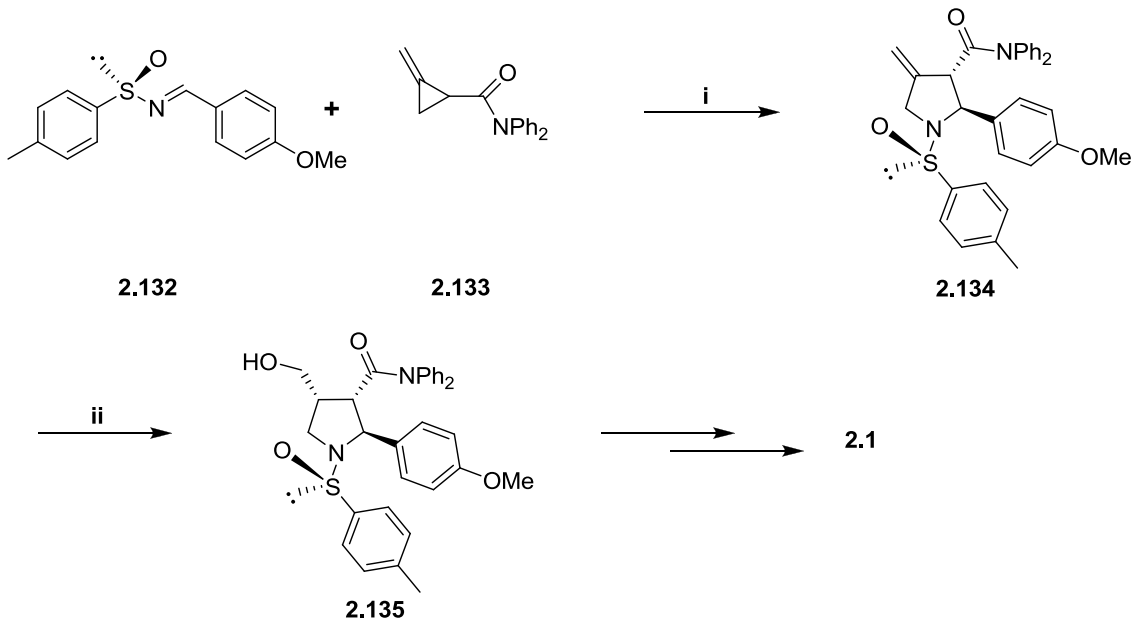

*Reagents and conditions*: i. (a) *n*-BuLi, (-)-Sparteine (2.2 eq.), toluene, -78 $^{o}$C, 1 h. (b) MeOH; *Cb* = C(O)N*i*-$Pr_2$;

**Scheme 2.26:** Hoppe's synthesis of kainic acid **2.1**.

Intramolecular *anti* $S_N'$ $S_E'$ cycloalkylation of (*E*,*E*)-carbamate **2.129**, commenced with $\alpha$-deprotonation by means of *n*-BuLi/(-)-sparteine at -78 $^{o}$C in toluene to give the pyrrolidine **2.130** as the major diastereomer (scheme 2.26). The C3-C4 *cis* pyrrolidine **2.130** would undergo further modifications to form kainic acid **2.1** in 7 subsequent steps.

### 2.1.4.20. Lautens's Synthesis[69]

Lauten in the year 2005, reported a concise and enantioselective synthesis of kainic acid **2.1** in 13 steps with an overall yield of 15%. The pyrrolidine **2.134** kainoid precursor was prepared by $MgI_2$-mediated ring expansion of *N*, *N*-diphenylmethylene-cyclopropyl amide **2.133** in the presence of a chiral sulfinimine **2.132** with the required C2/C3 trans stereochemistry (scheme 2.27). Hydroboration of the pyrrolidine **2.134** from the least hindered face using 9-BBN, followed by standard oxidative workup, afforded the alcohol **2.135** as a single diastereomer. This alcohol **2.135** provided the required stereochemistry for an en-route synthesis of kainic acid **2.1**.

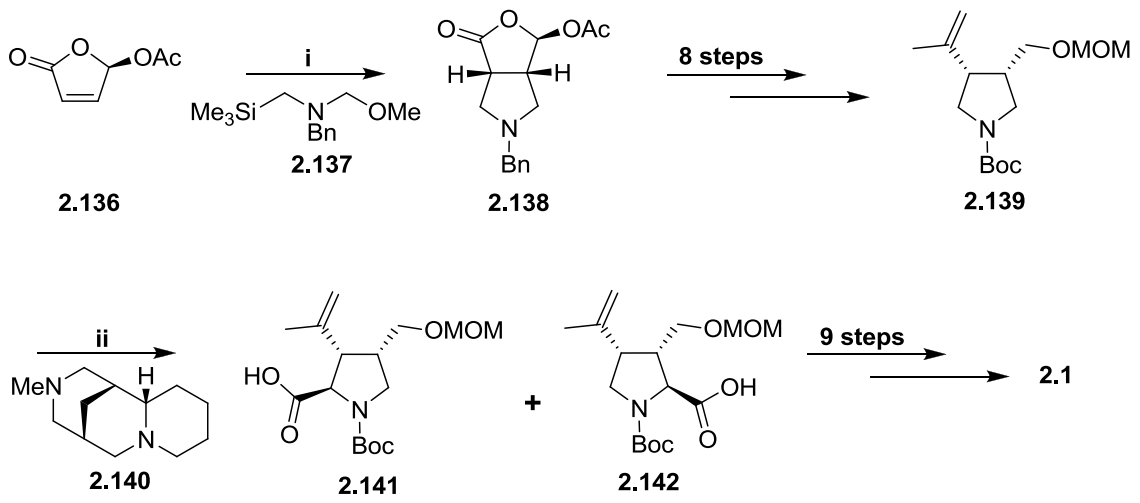



*Reagents and conditions*: i. $MgI_2$, THF (78%); ii. 9-BBN, THF, 50 $^oC$ then NaOH, $H_2O_2$ (91%);

**Scheme 2.27:** Lautens's synthesis of kainic acid **2.1**.

### 2.1.4.21. Fukuyama's synthesis

To date Fukuyama has produced four total synthesis of kainic acid **2.1.** The first total synthesis in the year 2005, involved regio- and stereoselective lithiation of the pyrrolidine ring **2.139** with the (+)-sparteine derivative **2.140** (scheme 2.28).[70] Cycloadduct **2.138** is formed by the 1,3-dipolar cycloaddition of the chiral butenolide **2.136** and azomethine ylide formed from **2.137** with high diastereoselectivity (20:1). The cycloadduct **2.138** is converted to the MOM protected pyrrolidine derivative **2.139** in 8 subsequent steps. Compound **2.139** on treatment with (+)-sparteine and *s*-BuLi at -78 $^{o}$C gave the trisubstituted pyrrolidine derivative as an inseparable mixture of regio- and diastereoisomers **2.141** and **2.142**.The undesired isomer was epimerised and the MOM group removed. This allowed separation of the regioisomers, with the desired isomer as major product in 2 steps in 63% yield.

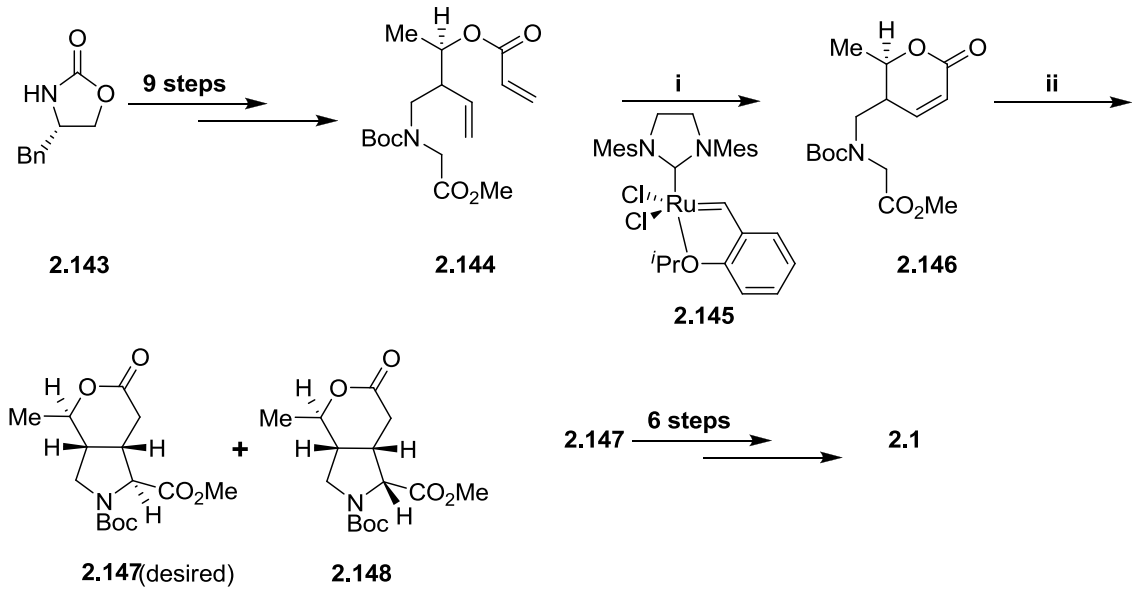



*Reagents and conditions*: i. **2.137**, TFA(10 mol %), DCM, 83%; ii. **2.140**, *s*-BuLi, THF, $CO_2$ (g), -78 $^{o}$C;

**Scheme 2.28:** Fukuyama's synthesis of kainic acid **2.1**.

In the year 2007, Fukuyama reported another total synthesis of kainic acid **2.1** by Ring-Closing Metathesis followed by an intramolecular Michael addition.[71] The metathesis of compound **2.144** was conducted using the Hoveyda-Grubbs' second-generation

catalyst[72] **2.145**. The use of 5 mol % of the catalyst in DCM at 80 $^{o}$C afforded the desired lactone **2.146** in 98% yield.

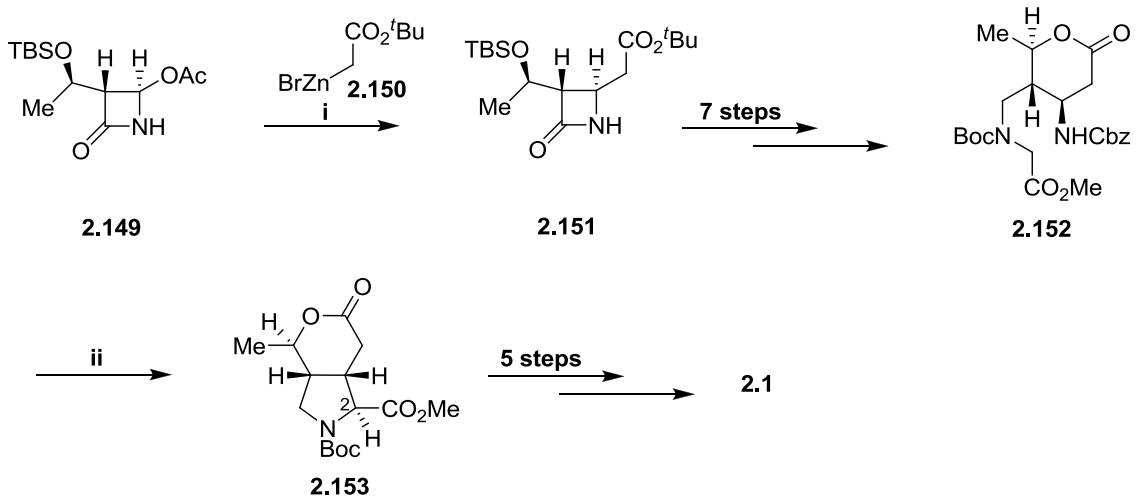



*Reagents and conditions*: i. Hoveyda-Grubbs' 2$^{nd}$ Generation Catalyst **2.145** (5 mol %), DCM, 80 $^{o}$C, 24 h, 98%; ii. KHMDS, toluene, -78 $^{o}$C, 89 %, (**2.147**: **2.148** = 71:29);

**Scheme 2.29:** Fukuyama's synthesis of kainic acid **2.1**.

The crucial Michael addition was achieved by treatment of **2.146** with KHMDS in toluene at -78 $^{o}$C to provide a mixture of the desired pyrrolidine derivative **2.147** and its C-2 epimer **2.148** in a 71:29 ratio (scheme 2.29). The pyrrolidine derivative **2.147** underwent further modification to form kainic acid **2.1** in 6 subsequent steps.

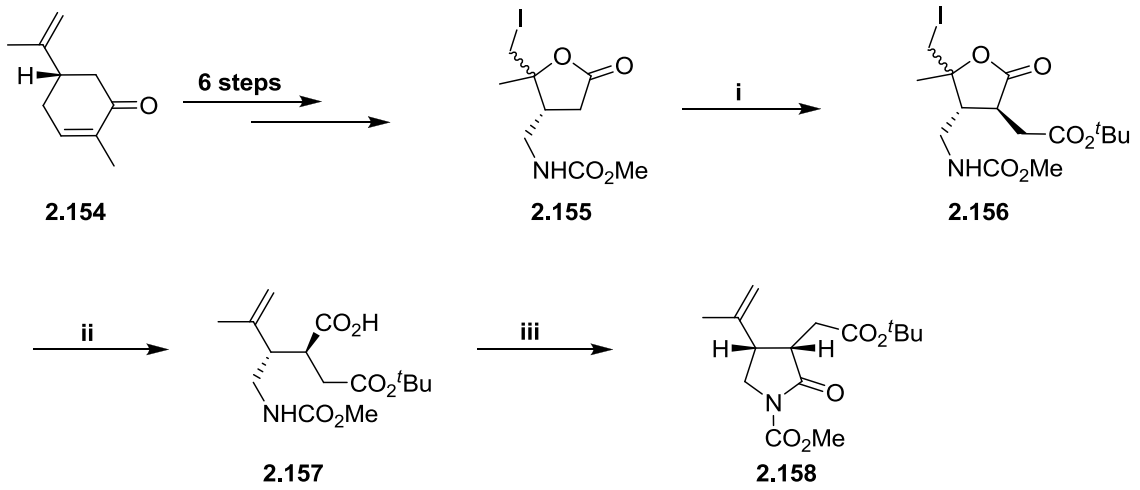
Similar to the above, another total synthesis of kainic acid **2.1** starting from the commercially available azetidinone **2.149** was described by Fukuyama[73] in the year 2008. Compound **2.151** was prepared through the Reformatsky-type[74] reaction from **2.149** using *t*-butyl bromozincacetate **2.150**. The desired *β*-amino-*δ*-lactone **2.152** was prepared in 7 subsequent steps from **2.151**.




*Reagents and conditions*: i. **2.150**, THF, 0 °C - rt, 12 h, 93%; ii. (a) LiHMDS, CbzCl, DMF, -60 °C - rt, 20 min, (b) LiHMDS, -60 °C, 20 min, 94%, **2.152**: C2-epimer = 92:8;

**Scheme 2.30:** Fukuyama's synthesis of kainic acid **2.1**.

Cyclisation of **2.152** took place smoothly to afford a diasteromeric mixture of the desired pyrrolidine derivative **2.153** and its C-2 epimer in 92:8 ratio (scheme 2.30). The pyrrolidine derivative **2.153** was converted to kainic acid **2.1** in a further 5 steps in 14% overall yield.



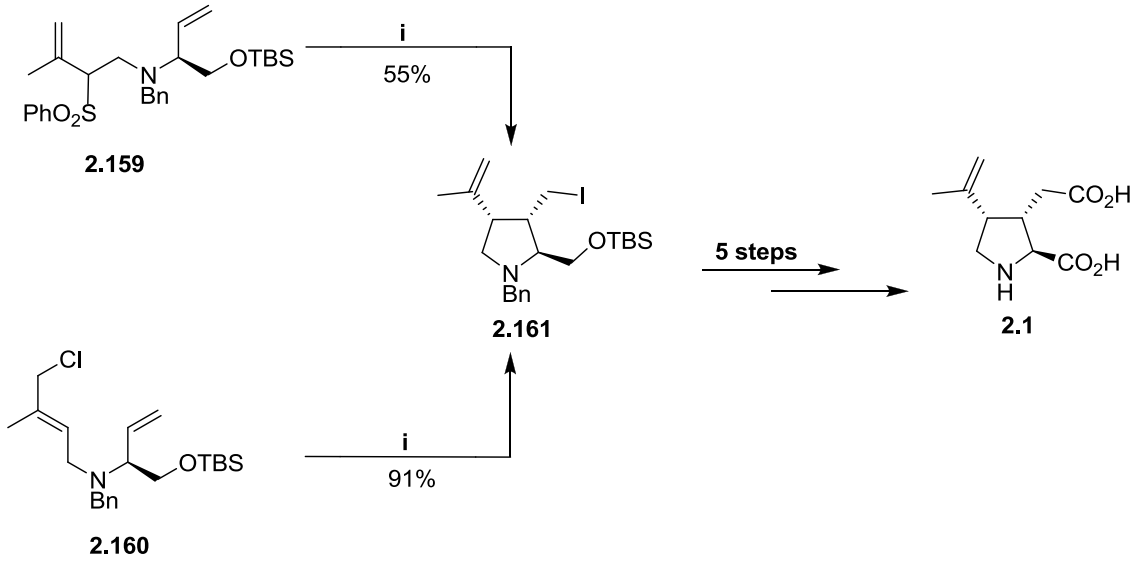

*Reagents and conditions*: i. LiHMDS, THF, -78 °C, $BrCH_2CO_2{}^tBu$, -78 °C, 82%; ii. Zn, AcOH, EtOH, 0°C - rt.; iii. DEPC, $Et_3N$, DCM, rt. 60% (2 steps);

**Scheme 2.31:** Fukuyama's synthesis of kainic acid **2.1**.

The most recent synthesis by Fukuyama was a practical stereoselective synthesis efficiently prepared from (+)-carvone **2.154**[75] in the year 2011. Iodolactone **2.155** was prepared in six steps starting from carvone **2.154**. Having developed iodolactone **2.155**, followed by addition of *tert*-butyl bromoacetate at -78 $^{o}$C furnished ester **2.156** in 82% yield. Carboxylic acid **2.157** was prepared by the reductive ring-opening reaction of the iodolactone moiety in **2.156** by treatment with Zn dust in the presence of acetic acid (scheme 2.31). The carboxylic acid **2.157** upon treatment with DEPC[76] and triethylamine at ambient temperature, underwent cyclization to afford the desired *cis*-substituted lactam **2.158**, which was further elaborated to give kainic acid **2.1** in 5 steps. Starting from 100 g of carvone **2.154** Fukuyama could get 14.6 g of kainic acid **2.1** in 10.3% overall yield.

### 2.1.4.22. Cohen's Synthesis[77]

Cohen reported the total synthesis of kainic acid **2.1** in the year 2007, which features a Pd-catalyzed Zn mediated cyclisation that proceeds with complete diastereoselectivity. Both cyclisation substrates **2.159** and **2.160** were prepared from the commercially available D-serine methyl ester hydrochloride.



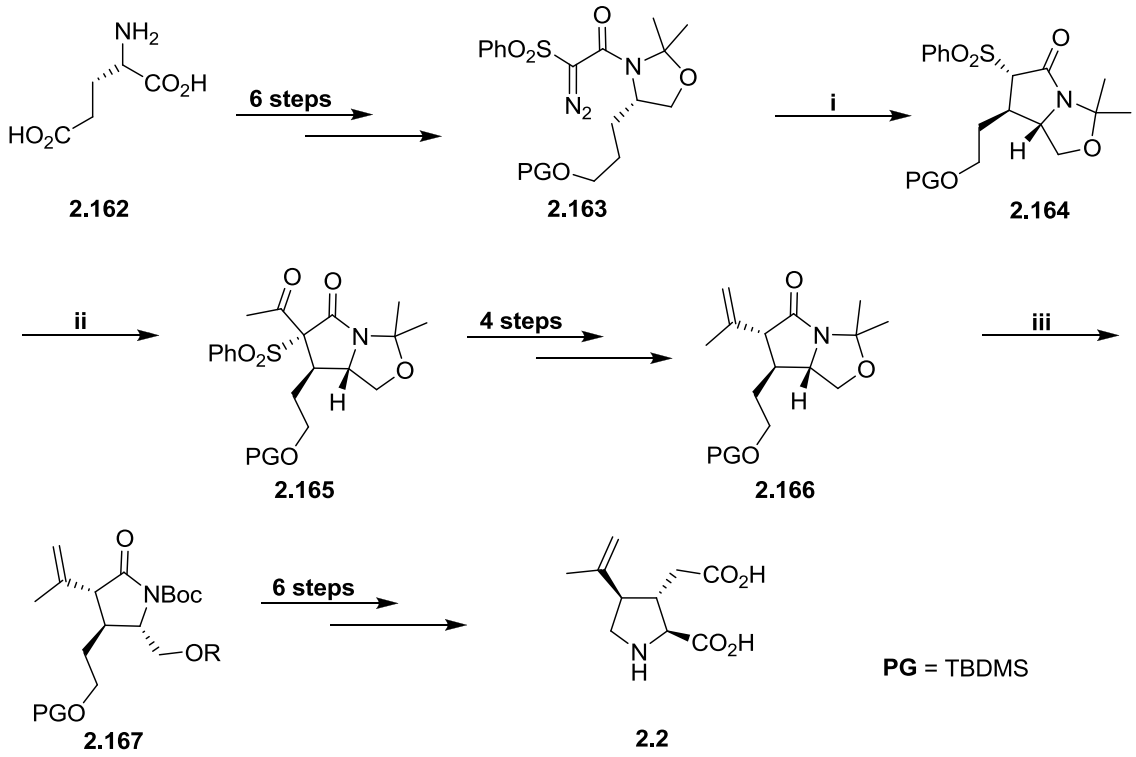

*Reagents and conditions*: i. (a) $Pd^{(0)}$, $ZnEt_2$. (b) $I_2$;

**Scheme 2.32:** Cohen's synthesis of kainic acid **2.1**.

The Pd-catalyzed Zn-ene cyclization of **2.159** provided pyrrolidine **2.161** in a 55% yield as a single diastereomer (scheme 2.32). The cyclisation of diene **2.160** provided, pyrrolidine **2.161** in 91% yield as a single diastereomer. Pyrrolidine **2.161** undergoes further modifications in 5 steps to give kainic acid **2.1**.

### 2.1.4.23. Jung's Synthesis[78]

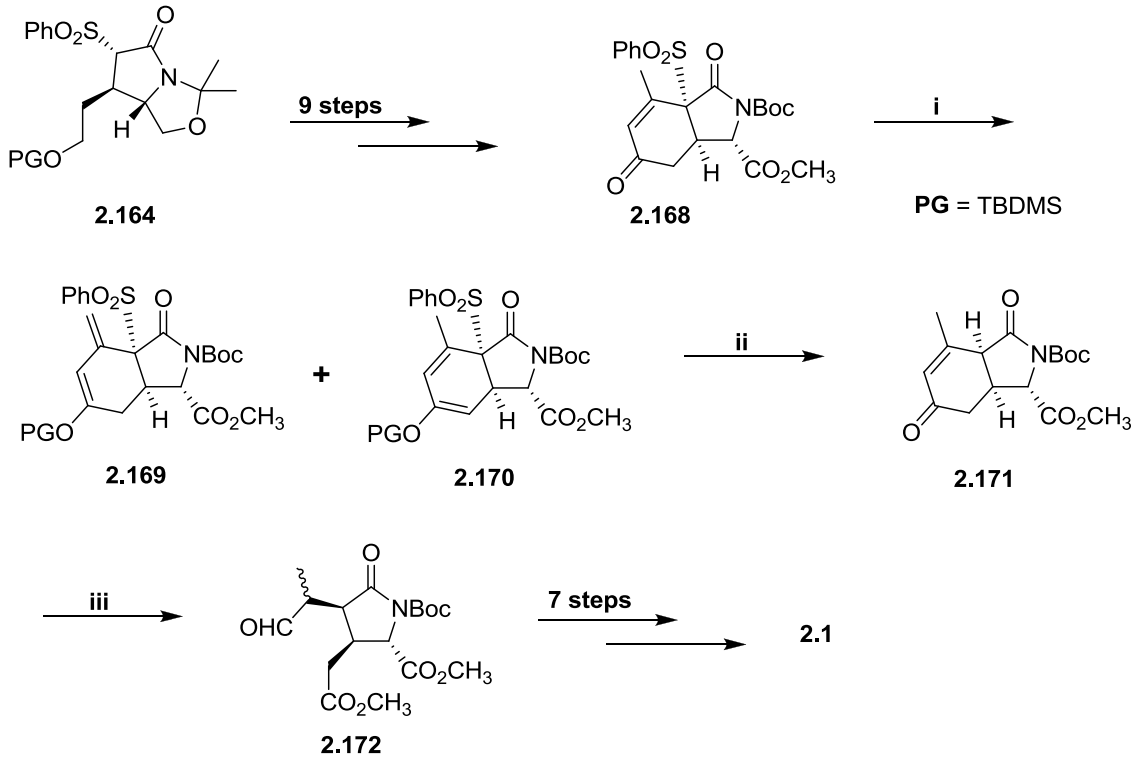
K. W. Jung in the year 1997, reported a novel approach to the total synthesis of (–)-$\alpha$-kainic acid **2.1** and (+)-$\alpha$-allokainic acid **2.2**, wherein a regio- and stereoselective C-H insertion reaction was utilized to prepare the $\gamma$-lactam **2.164** as an intermediate.




*Reagents and conditions*: i. $Rh_2(OAc)_4$, DCM, 92%; ii. $Ac_2O$, NaH, THF, 98%; iii. (a) Dowex 50W-8X. (b) TBDMSCl, DMAP, TEA, DCM. (c) $Boc_2O$, TEA, DCM, 70%;

**Scheme 2.33:** Jung's synthesis of allokainic acid **2.2**.

The C-H insertion precursor **2.163** was prepared from L-glutamic acid **2.162** over 6 steps. A Rh(II) catalyzed intramolecular C-H insertion of diazo compound **2.163** then gave the desired trans- $\gamma$-lactam **2.164** as a single isomer in 92% yield with excellent regio- and stereoselectivity. Acetylation of the phenylsulfone of **2.164** was carried out efficiently, using $Ac_2O$ and NaH in THF to give acetyl compound **2.165** (scheme 2.33). The *trans* intermediate **2.166**, was prepared from acetyl compound **2.165** in 4 steps. After the successful isolation of *trans*-C6, C7 conformational product **2.166**, the acetonide in compound **2.166** was unmasked, and subsequent Boc protection furnished trisubstituted pyrrolidone **2.167**, which would give allokainic acid **2.2** in further 6 steps.




*Reagents and conditions*: i. TBSOTf, TEA, DCM, 99%; ii. Na/Hg, THF/MeOH, 98%; iii. (a) *m*-CPBA, DCM, 65%. (b) NaOMe, MeOH, -78 $^{o}$C, 85%;

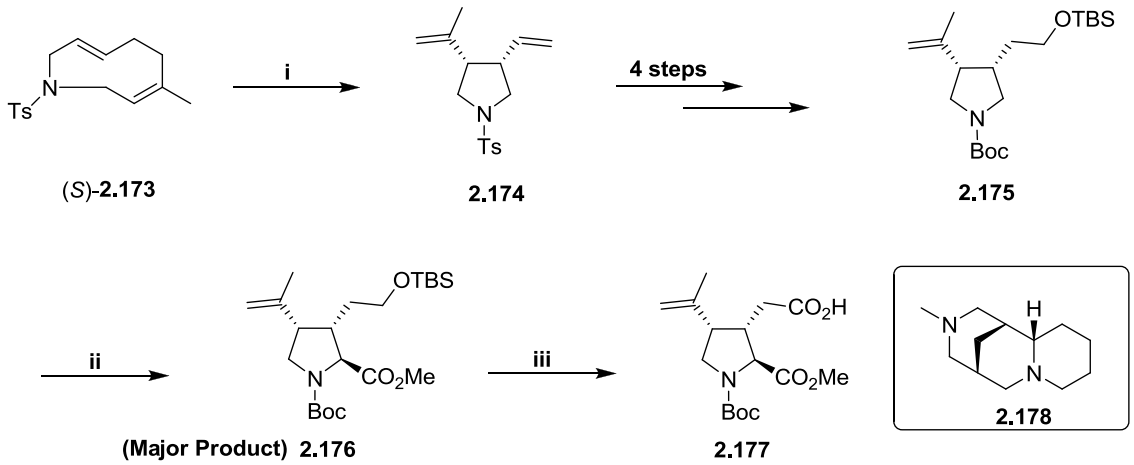
**Scheme 2.34:** Jung's synthesis of kainic acid **2.1**.

Utilizing compound **2.164**, a new strategy for the stereoselective installation of the *cis*-C3, C4 relationship to achieve the synthesis of kainic acid **2.1** was proposed. The ester compound **2.168** was formed in 9 steps from **2.164** (scheme 2.34). Silylation of

cyclohexenone **2.168** using TBSOTf in the presence of TEA gave a mixture of two isomers **2.169** and **2.170** in a ratio of 2:1. The mixture of both the isomers were subjected to reduction conditions using Na/Hg at -20 $^{o}$C to provide only one diastereomer in 98% yield. Here during the dephenylsulfonylation, deprotection of TBDMS group took place to yield cyclohexenone **2.171**. The cyclohexenone **2.171** underwent a Baeyer-Villiger oxidation, followed by a ring opening of the enol lactone formed using NaOMe at -78 $^{o}$C in two steps to give the aldehyde ester compound **2.172**. This on further modification gives kainic acid **2.1** as the final product in 7 steps.

### 2.1.4.24. Suzuki's Synthesis[79]

An asymmetric synthesis of (±)-kainic acid **2.1** using a planar chiral amide as a chiral building block was reported by Masaki Suzuki. The requisite amide (*S*)- **2.173** was prepared by a previously developed method,[80] which underwent a subsequent Cope rearrangement in the presence of Pd(II) to yield (*3S*, 4*S*)- **2.174** as the sole product in 87% yield. Diene **2.174** underwent deprotection, reprotection and oxidation of double bond in 4 steps to give TBS protected alcohol **2.175**.



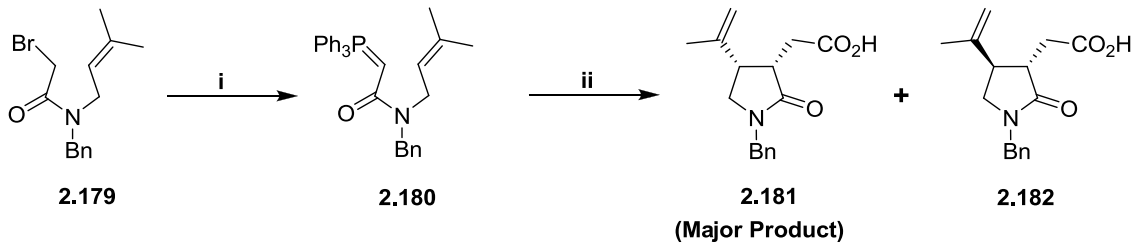

*Reagents and conditions*: i. cat. $PdCl_2(PhCN)_2$, DCM, rt, 87%; ii. *s*-BuLi, **2.178**, $Et_2O$, -78 $^{o}$C then ClCOOMe, -78 $^{o}$C, 84%; iii. Jones reagent, acetone, 0 $^{o}$C – rt;

**Scheme 2.35:** Suzuki's synthesis of kainic acid **2.1**.

Lithiation of **2.175** using *s*-BuLi/**2.178** followed by reaction with methylchloroformate, provided the desired C-2 carboxylation compound as the major product **2.176** in excellent stereoselectivity (49%, >98% dr). **2.177** was formed by the treatment of **2.176** with Jones reagent[81] via a sequential deprotection of the TBS group and oxidation of the resulting primary alcohol on the C3 side chain (scheme 2.35). **2.177** on subsequent 3 steps gave the desired kainic acid **2.1**.

### 2.1.4.25. Tilve's Synthesis[82]

A tandem Wittig-intramolecular ene reaction approach was proposed by Santosh G. Tilve in the year 2009. *N*,*N*-disubstituted bromoacetamide **2.179** was prepared by the N-alkylation of benzylamine with prenyl bromide in the presence of $K_2CO_3$ followed by the treatment of monoalkylated benzylamine with bromoacetyl bromide. Reaction of bromoacetamide **2.179** with $PPh_3$ gave the corresponding Wittig salt, which on deprotonation using NaOH provided the required phosphorane **2.180** in good yield (scheme 2.36).




**2.179** **2.180** **2.181** (Major Product) **2.182**

*Reagents and conditions*: i. (a) $PPh_3$, $C_6H_6$. (b) 2N NaOH, 86%; ii. 50% aq. CHOCOOH, toluene, 110 $^oC$, 24 h, **2.181**: **2.182** = 20:1, 60%;

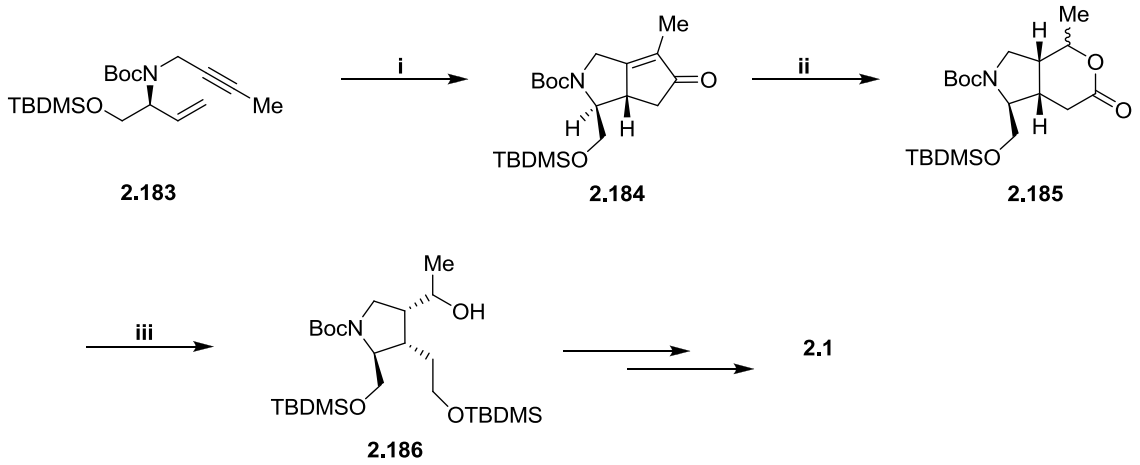
**Scheme 2.36:** Tilve's synthesis of kainic acid **2.1**.

Phosphorane **2.180** was heated at reflux with glyoxalic acid in toluene, two reactions, the Wittig reaction and the intramolecular ene reaction, took place in a tandem fashion, yielding the desired product **2.181** and its *trans* analogue **2.182** as a minor product. The

compound **2.181** undergoes further modifications in 4 steps to give kainic acid **2.1** in 73% yield starting from **2.181**.

### 2.1.4.26. Helmchen's Synthesis[83]

An enantioselective total synthesis of kainic acid **2.1** was described by Günter Helmchen in the year 2010, which included key steps as an Ir-catalysed allylic amination, a diastereoselective intramolecular Pauson-Khand and Baeyer-Villiger reactions. The 1,6-enyne **2.183** was prepared by an Ir-catalysed allylic amination with a propargylic amine. The key cyclopentenone intermediate **2.184** was prepared from the 1,6-enyne **2.183** using a protocol of intramolecular Pauson-Khand reaction with 65% yield (scheme 2.37). The cyclopentenone **2.184** undergoes catalytic hydrogenation, followed by subsequent Baeyer-Villiger rearrangement with *m*-CPBA to give the lactone **2.185**. Reduction of lactone **2.185 (**scheme 2.37) furnished the monoalcohol **2.186** which has the required stereocenters for the total synthesis of kainic acid **2.1**.

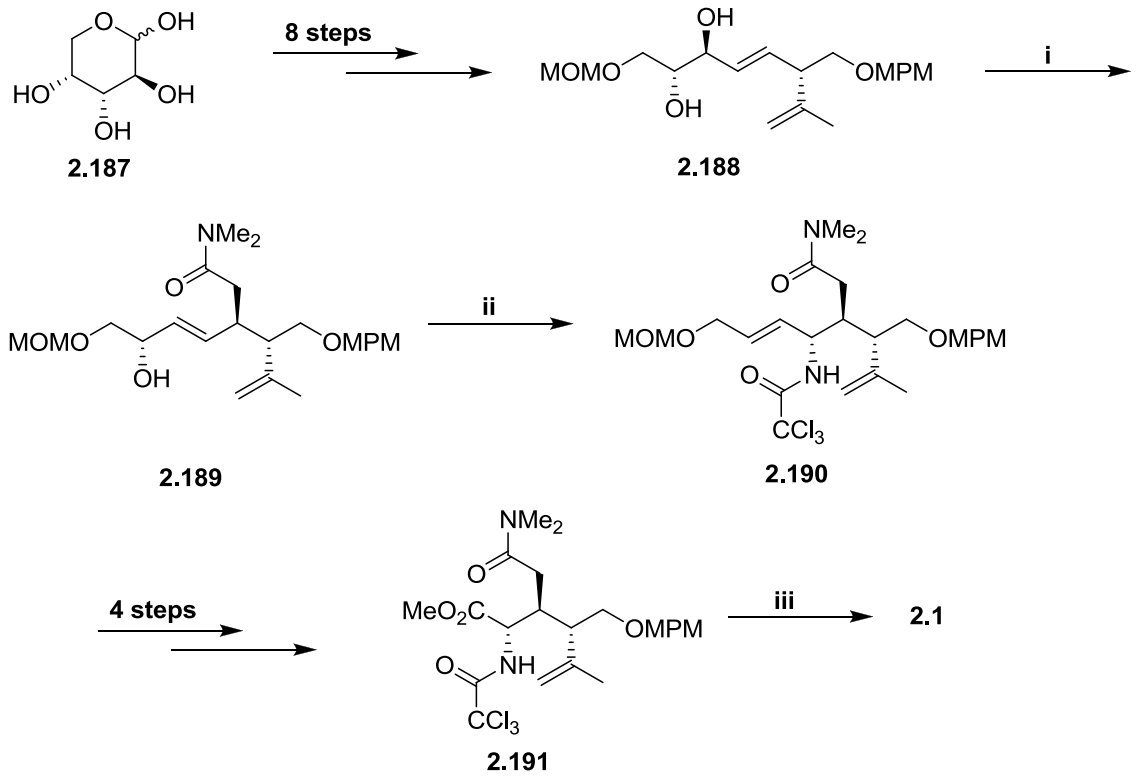



*Reagents and conditions*: i. (a) $Co_2(CO)_8$ (1.1 eq) DCM, rt, 4 h. (b) $Me_3NO{\cdot}2H_2O$ (6.8 eq) 4Å MS, rt, 4 h, 65%; ii. (a) $H_2$ (5 bar) $Pd(OH)_2/C$ (10 wt%) EtOAc, rt, 20 h (97%). (b) *m*-CPBA (2.5 eq) $Na_2HPO_4$ (25 eq) DCM, rt, 9 h (86%); iii. (a) $CaCl_2$ (3 eq), $NaBH_4$ (6 eq) EtOH, 50 $^oC$, 4 h. (b) TBDMSCl (1.1 eq) imidazole (2 eq) DCM, rt, 5.5 h, 92%;

**Scheme 2.37:** Helmchen's synthesis of kainic acid **2.1**.

### 2.1.4.27. Chida's Synthesis[84]

In the year 2010, Noritaka Chida and co-workers successfully applied a sequential Claisen/Overman rearrangement to the total synthesis of kainic acid **2.1**(scheme 2.38). *E*-Allylic *anti*-diol **2.188** was prepared in a series of steps by the use of chirality transfer of the three secondary hydroxyl groups embedded in D-arabinose **2.187**. The crucial sequential Claisen rearrangement of **2.188** and the subsequent Overman rearrangement of **2.189** proceeded with complete diastereoselectivity, giving the trichloroacetamide **2.190**. This key acyclic intermediate **2.190** underwent a chemoselective oxidative cleavage in further 4 steps to provide methyl ester **2.191** in 38% yield (3 steps).



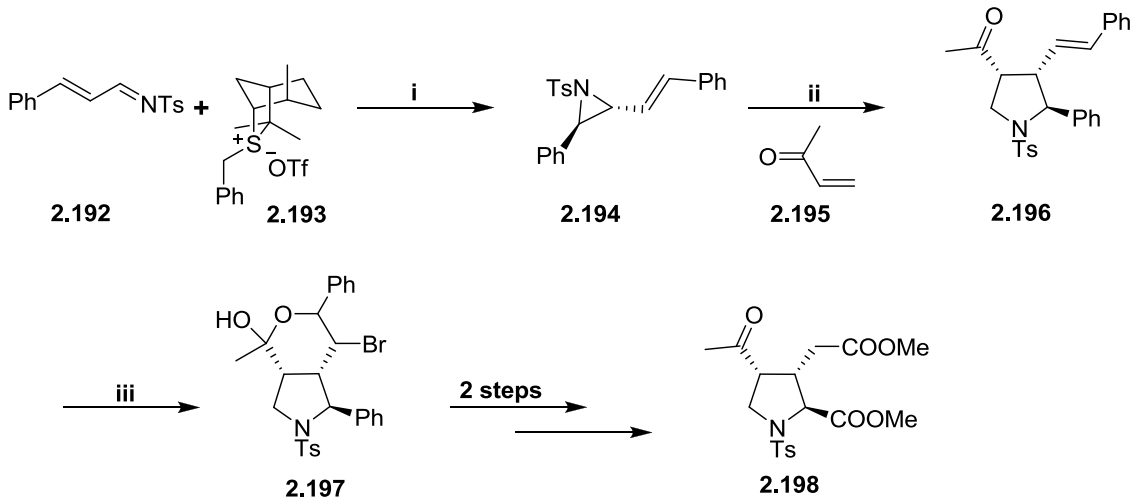

*Reagents and conditions*: i. $MeC(OMe)_2NMe_2$, toluene, MS4Å, 140 $^oC$ in a sealed tube, 70%; ii. (a) $CCl_3CN$, DBU, DCM, rt. (b) $K_2CO_3$, toluene, 120 $^oC$ in a sealed tube, 72% (2 steps); iii. (a) CAN, $MeCN/H_2O$, rt, 91%. (b) DEAD, $PBu_3$, THF, 0 $^oC$, 88%. (c) KOH, $^tBuOH/H_2O$, 120 $^oC$, 75%;

**Scheme 2.38:** Chida's synthesis of kainic acid **2.1**.

The methyl ester **2.191** undergoes cleavage of the MPM (or PMB) group with CAN, followed by a Mitsunobu reaction and overall deprotection to accomplish the total synthesis of (–)- kainic acid **2.1**.

### 2.1.4.28. Aggarwal's Synthesis[85]

A formal synthesis of kainic acid **2.1** by the palladium-mediated annulation of vinyl aziridines with Michael acceptors was reported by Varinder K. Aggarwal in the year 2011. Vinyl aziridine **2.194** was prepared by the diastereoselective aziridination of imine **2.192** using chiral sulphur ylide[86] **2.193**. Palladium-catalysed annulation of **2.194** with methyl vinyl ketone **2.195** furnished pyrrolidine **2.196** in good yield and high diastereoselectivity. Convertion of styryl group of pyrrolidine **2.196** into a carboxylic ester **2.198** was achieved through the halohydrin **2.197** which further undergoes radical debromination, oxidation and esterification (scheme 2.39). The ester **2.198** in further 3 steps gives kainic acid **2.1**.

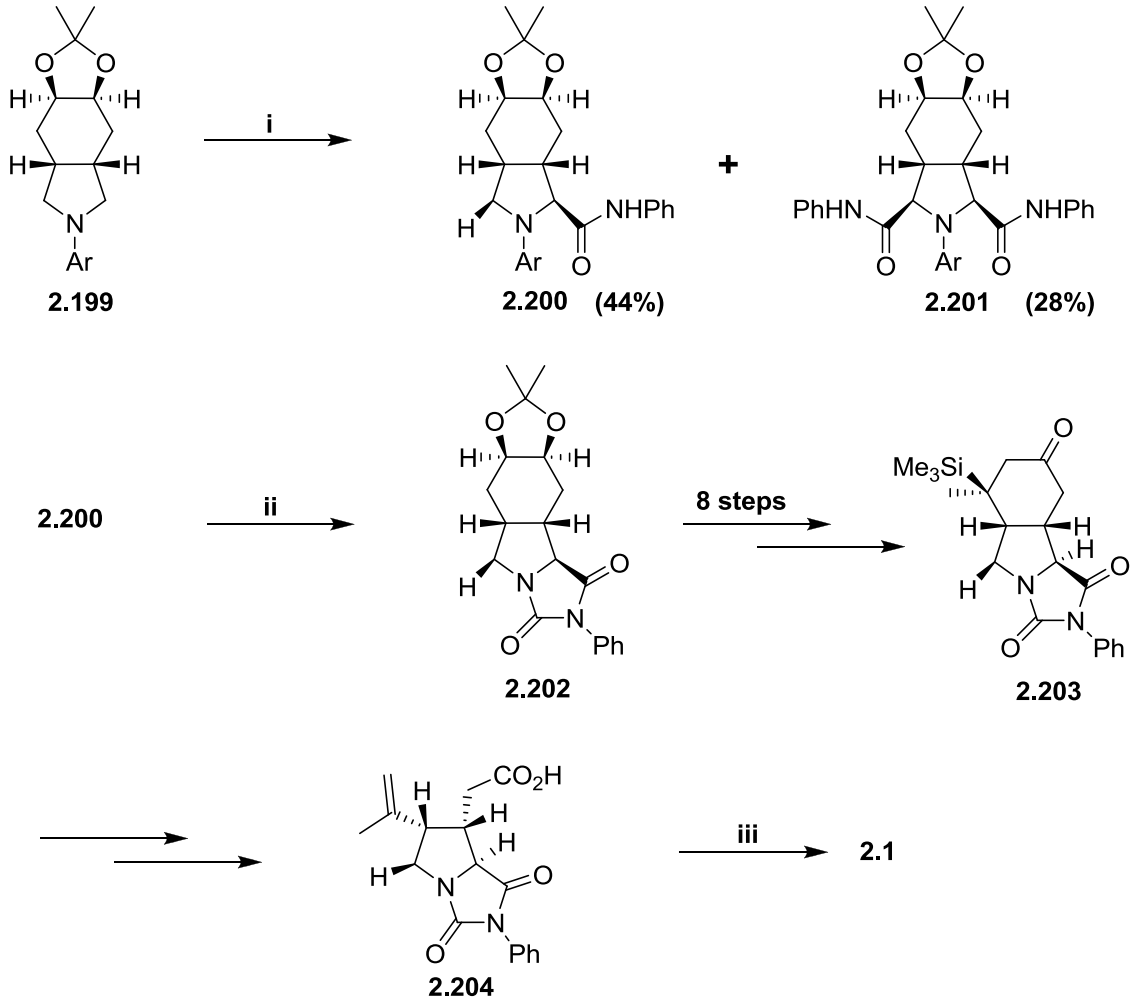



*Reagents and conditions*: i. $NaHCO_3$, $CH_3CN$, rt, 85%, 99% ee; ii. $[Pd_2(dba)_3{\cdot}CHCl_3]$, $n$$Bu_4NCl$, P(*o*-tolyl)$_3$, pentane, 62%; iii. NBS, $H_2O$, acetone, rt, 95%;

**Scheme 2.39:** Aggarwal's synthesis of kainic acid **2.1**.

### 2.1.4.29. Yoshimitsu Synthesis[87]

Recently in the year 2011, Takehiko Yoshimitsu performed a novel photochemical C-H carbamoylation of an *cis*-fused azabicyclo[4.3.0]nonane **2.199** with PhNCO to provide a highly functionalized anilide **2.200** which could be used to synthesise kainic acid **2.1**. The *cis*-fused azabicyclo[4.3.0]nonane **2.199** was prepared in four steps from the commercially available tetrahydromaleic anhydride.[88] Photolysis of **2.199**, at short-wavelength light (<300 nm), in the presence of a photosensitizer 4,4′-dimethoxybenzophenone gave anilide **2.200** along with the disubstituted compound **2.201**.



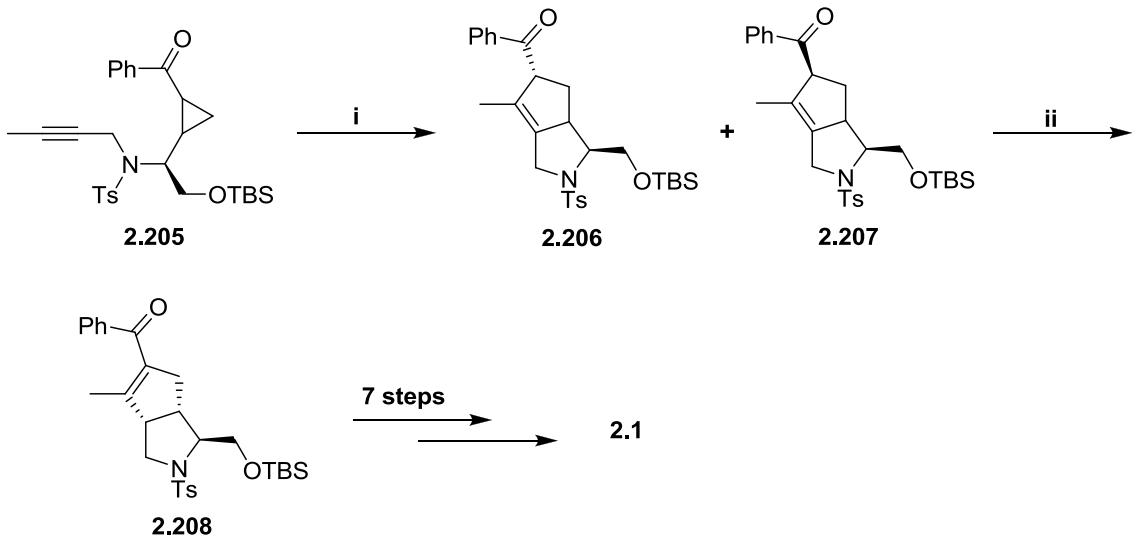

*Reagents and conditions*: i. PhNCO, 4,4′-dimethoxybenzophenone, hν, MeCN, rt, 8.5 h; ii. (a) CAN, aq MeCN, 0 $^{o}$C. (b) CDI, DMAP, THF, 60 $^{o}$C, 65% in 2 steps; iii. 3 *N* NaOH, reflux then ion-exchange resin;

**Scheme 2.40:** Yoshimitsu's synthesis of kainic acid **2.1**.

Yashimitsu reported this, as the first example of an intermolecular addition of a photochemically generated $\alpha$-amino alkyl radical to phenyl isocyanate to furnish amino acid anilides (scheme 2.40). Anilide **2.200** was treated with CAN in aqueous MeCN at ambient temperature followed by protection of the resultant amine to furnish tetracyclic **2.202** in 65% yield in 2 steps. Further hydrolysis of **2.202**, followed by dehydration, Dess-Martin oxidation, methylation and 1,4-silylation to give silylated ketone **2.203** in 8 subsequent steps. The compound **2.203** undergoes Baeyer-Villiger oxidation, followed by desilylation in two steps to give the precursor olefin **2.204**. Hydrolysis of **2.204**, gave kainic acid **2.1** as the sole product.

### 2.1.4.30. Li's Synthesis[89]

Li in the year 2012, reported an enantioselective synthesis of kainic acid **2.1** *via* $SmI_2$-catalysed intramolecular [3+2] cycloaddition reaction. As in previous synthesis, the cyclisation substrate **2.205** was derived from the commercially available D-serine methyl ester hydrochloride.



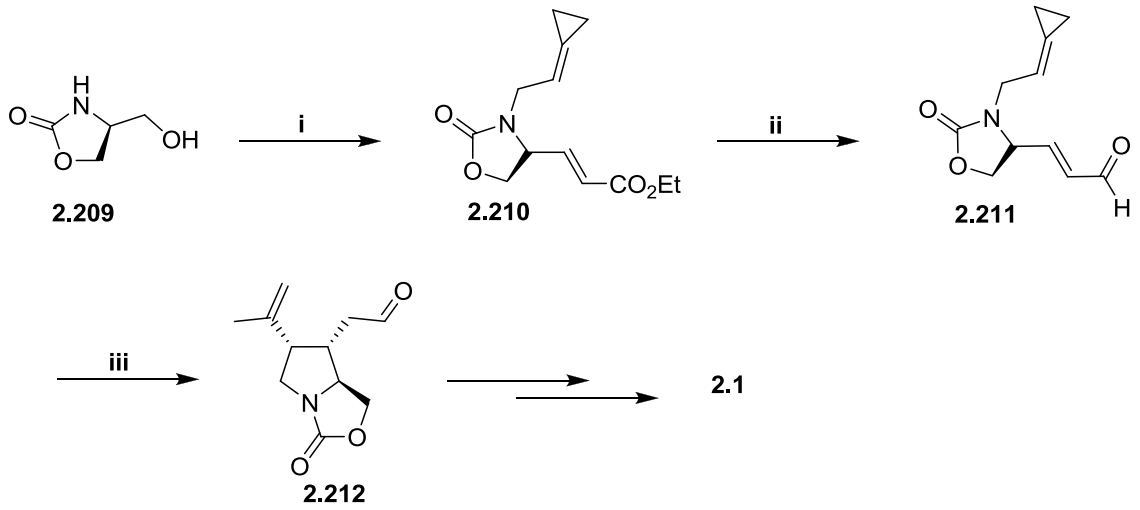

*Reagents and conditions*: i. $SmI_2$ (2.5 eq.), THF, rt, 81%; ii. DBU, THF, reflux, 95%;

**Scheme 2.40:** Li's synthesis of kainic acid **2.1**.

Substrate **2.205** undergoes cycloaddition with $SmI_2$ in THF to afford bicyclic products **2.206** and **2.207** in 81% yield (scheme 2.40) with excellent diastereoselectivity (**2.206**: **2.207** = 12:1). Treatment of **2.206** and **2.207** with DBU isomerised the double bond to give the bicyclic enone **2.208** in 95% yield. The enone **2.208** undergoes further modification to give kainic acid **2.1** in 7 subsequent steps.

### 2.1.4.31. Evans's synthesis[90]

Recently in the year 2012, Evans proposed a diastereoselective rhodium-catalysed ene-cycloisomerisation reaction of alkenylidenecyclopropane to the total synthesis of kainic acid **2.1**.




*Reagents and conditions*: i. (a) DMP, pyridine, $Ph_3PCHCO_2Et$, DCM/MeCN, 40 $^oC$, 77%. (b) 1-Vinylcyclopropyl tosylate, cat. $Pd(PPh_3)_4$, THF, then pronucleophile, NaH, THF, rt, 84%; ii. DIBAL-H, $BF_3{\cdot}OEt_2$, DCM, -78 $^oC$ – rt, 70%; iii. $[Rh(COD)Cl]_2$ (4 mol%), tri-*p*-tolyl phosphate (24 mol %), THF, 135 $^oC$ (sealed tube), 69%;

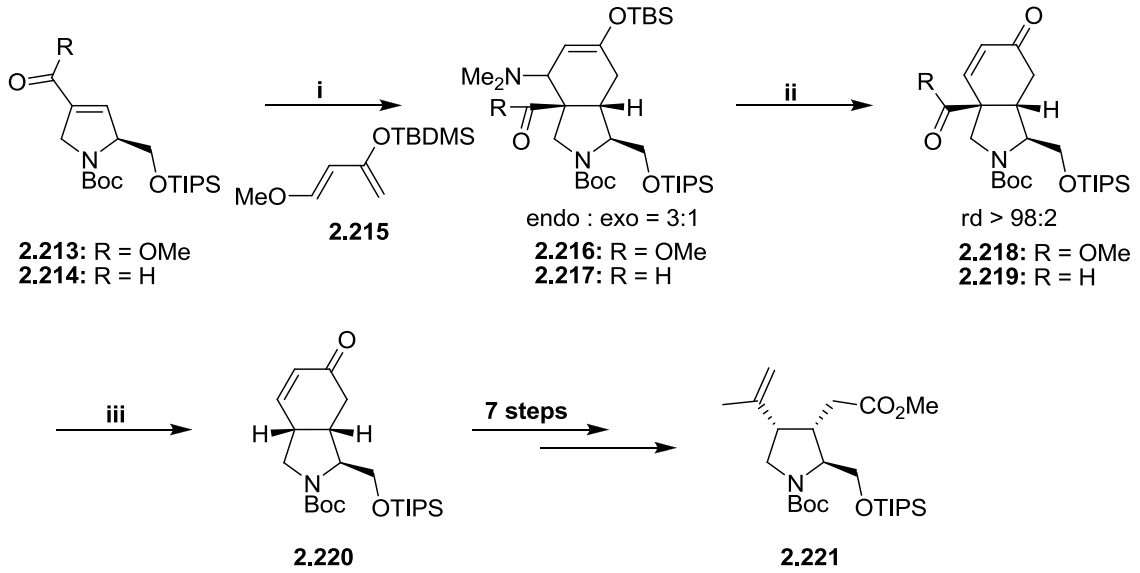
**Scheme 2.41:** Evan's synthesis of kainic acid **2.1**.

Commercially available amino alcohol **2.209** was subjected to one-pot sequential Dess-Martin oxidation, followed by a concomitant Wittig homologation to give the conjugated ester in 77% yield, which further underwent palladium-catalysed allylic amination to afford $\alpha,\beta$-unsaturated ester **2.210** in 84% yield.[91] DIBAL-H reduction of

ester **2.210** afforded allylic alcohol **2.211** in 70% yield. The key rhodium-catalysed ene-cycloisomerisation reaction of **2.211** with rhodium complex furnished *anti*,*syn*-2,3,4-trisubstituted pyrrolidine skeleton **2.212** in 69% yield(scheme 2.41) with excellent diastereocontrol(*ds* ≥ 19:1). The compound **2.212** undergoes further modification in 4 subsequent steps to give kainic acid **2.1**. The total synthesis of kainic acid **2.1** was accomplished by Evan in 8 steps from **2.209** in 17% overall yield.

### 2.1.4.32. Poisson's Synthesis[92]

Poisson in the year 2012, reported a Diels-Alder-based total synthesis of kainic acid 2.1. Enone 2.213 and 2.214 were prepared in 9 steps from commercially available hydroxyproline in 70% overall yield.

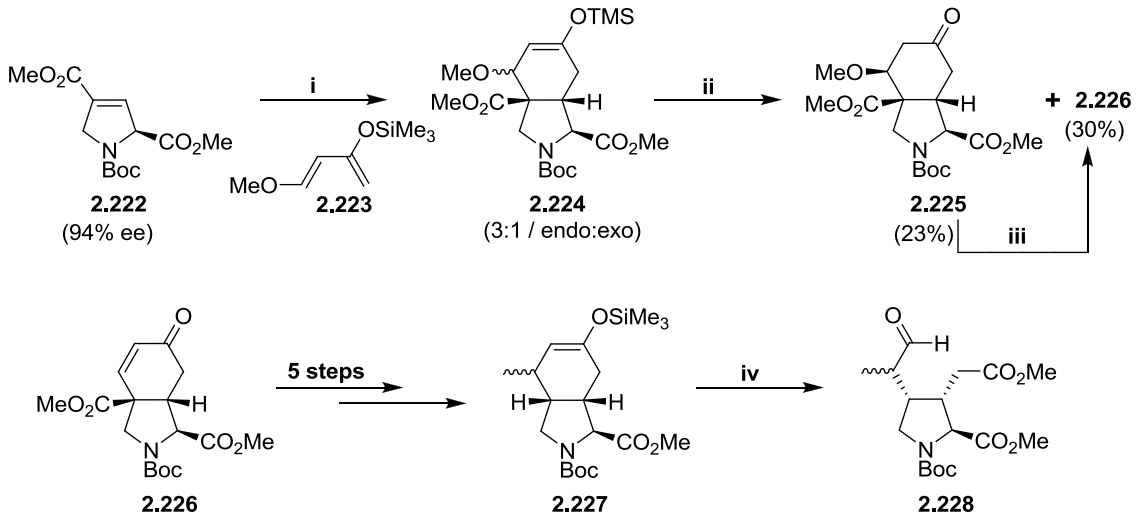



*Reagents and conditions*: i. **2.215**, toluene, Δ or THF, rt; ii. HCl (1M); iii. (a) **2.218**, LiOH, $NEt_3$, toluene 30% (from **2.213)**. (b) **2.219**, KOH/THF, 31% (from **2.214**);

**Scheme 2.42:** Poisson's synthesis of kainic acid **2.1**.

The *α*,*β*-unsaturated ester **2.213** and aldehyde **2.214** showed similar behaviour towards electron-rich dienes. In refluxing toluene, ester **2.213** and aldehyde **2.214** reacted with Rawal's diene[87] to give corresponding cycloadducts **2.216** and **2.217** (scheme 2.42). Hydrolysis of cycloadducts **2.216** and **2.217** provided only enones **2.218** and **2.219**

respectively. *β*-keto ester **2.218** on saponification, followed by decarboxylation of the resultant acid, provided enone **2.220** in 4 steps with 30% overall yield. *β*-keto aldehyde on decarbonylation with KOH gave the same enone **2.220** in 3 steps with 31% overall yield. The enone **2.220** undergoes further modification in 7 subsequent steps to give the precursor olefin **2.221**, which has the required stereocenters for the total synthesis of kainic acid **2.1**.



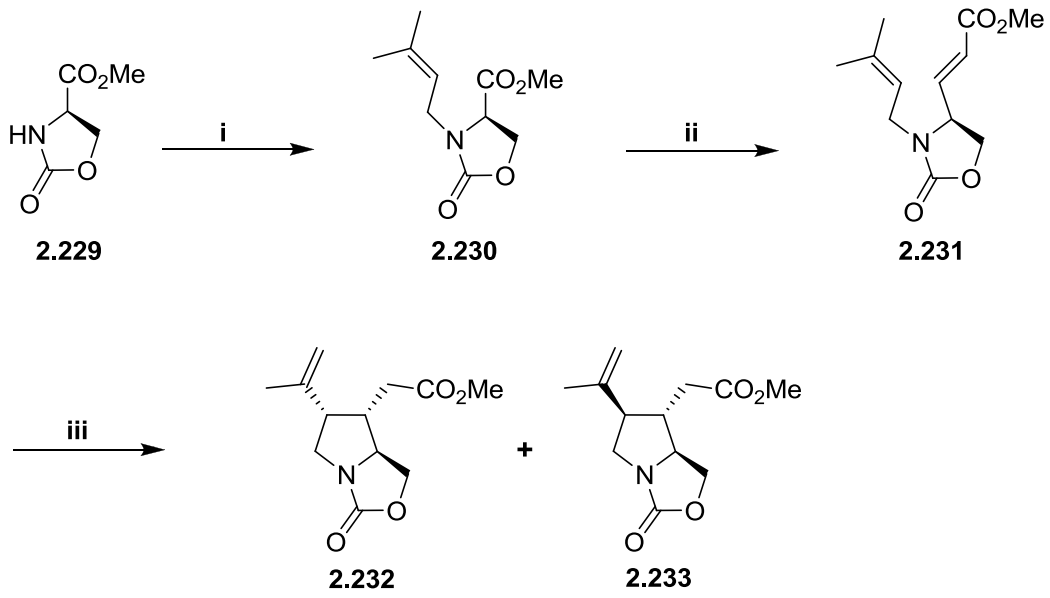

*Reagents and conditions*: i. **2.223**, DCM, 15 kbar; ii. $KHSO_4$ aq, THF; iii. DBU, toluene, 81%; iv. (a) $O_3$, -116 $^oC$, DMS. (b) $CH_2N_2$, 70% (3 steps);

**Scheme 2.43:** Poisson's synthesis of kainic acid **2.1**.

Similar to the (scheme 2.42) Poisson attempted high pressure [4 + 2] cycloaddition of ester **2.222** with Danishefsky's diene[87] **2.223**. The cycloadditon of ester **2.222** with diene **2.223** in DCM, at room temperature under 15 kbar after 82h gave the cycloadduct **2.224** in 96% yield (scheme 2.43). The cycloadduct **2.224** was converted into a mixture of **2.225** and the enone **2.226** by treatment with $KHSO_4$. The compound **2.225** was converted to **2.226** by treatment with DBU in hot toluene. The enone **2.226** was converted to unstable trimethylsilyl ester **2.227** in 5 steps.[87] The unstable compound **2.227** was ozonolysed at low temperature followed by reaction with diazomethane to give aldehyde diester **2.228** in 3 steps with 70% overall yield. The diester **2.228** has the required stereocenters for the total synthesis of kainic acid **2.1**.

### 2.1.4.33. Parsons Synthesis[93]

In an effort to produce new synthetic routes to the kainoids family, kainic acid was synthesised by Parsons and co-workers by using amino acid chemistry. It started with D-serine methyl ester, which was treated with triphosgene to afford the ester **2.229** quantitatively. N-alkylation of the ester **2.229** with 1-bromo-3-methyl-2-butene in the presence of sodium hydride gave the *N*-alkylated ester **2.230** in 78% yield. The compound **2.230** was reduced, to give aldehyde, which under Wittig reaction conditions gave the unsaturated ester **2.231**.




**2.229** **2.230** **2.231**

**2.232** **2.233**

*Reagents and conditions*: i. NaH, THF + DMF (4:1), 1-bromo-3-methyl-2-butene, 0 $^{o}$C – rt, 78%; ii. DIBAL-H, $CH_2Cl_2$, -78 $^{o}$C, followed by $NH_4Cl$ $(C_6H_5)_3P{=}CHCO_2CH_3$, –20 $^{o}$C, (83%); iii. MW, diethylaniline, 200 $^{o}$C, 4 h (80% 7:1 in favour of **2.232**);

**Scheme 2.41:** Parsons's synthesis of kainic acid **2.1**.

The solution of the unsaturated ester **2.231** was heated in diethylaniline at 200 $^{o}$C in a microwave to give the ene-product **2.232** and an allo-kainate precursor **2.233** in 80% yield with a diastereomeric ratio of 7:1 favoring **2.232**. The ene-product **2.232** has the required stereocenters for the total synthesis of kainic acid **2.1**(scheme 2.41). The total synthesis of kainic acid **2.1** was completed with 20% overall yield.

# 3. Results and Discussion

# 3.1. Introduction

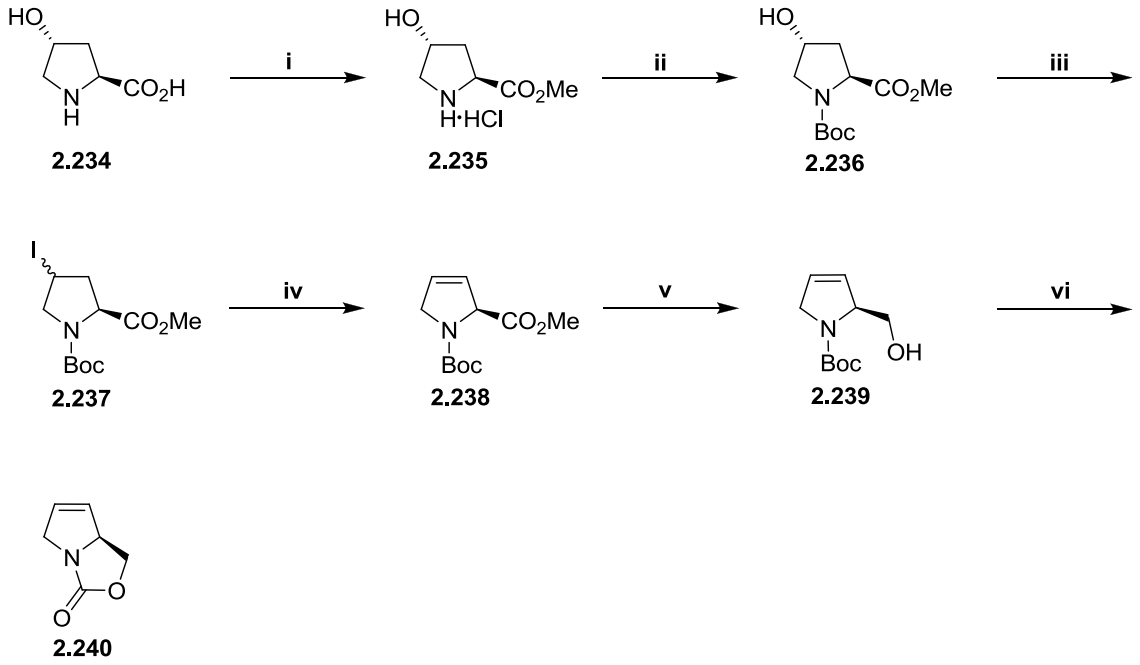
Following on from the previous work of Greenwood[94], Adrian Murray[95] and Jason Lai[96] it was the aim of the project to:

1) Further improve upon the previously developed procedure for the preparation of multi-gram quantities of oxazolidinone **2.240**.
2) Further investigate the diastereofacial selectivity of the oxazolidinone precursor **2.240**.
3) Using the oxazolidinone precursor **2.240**, to find a novel route to the total synthesis of (–)-kainic acid **2.1**.
4) Using the same precursor **2.240** for an attempted total synthesis of allokainic acid **2.2** and members of the other kainoid family.

## 3.1.1. Chemistry of the precursor oxazolidinone 2.240.

### 3.1.1.1. Formation of oxazolidinone 2.240:

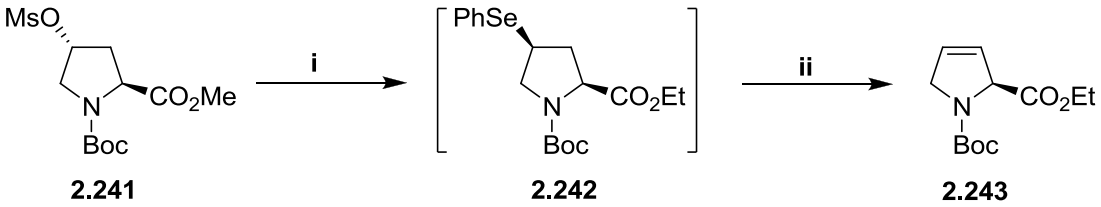
A modified procedure developed by Jason Lai[96] was used for the formation of the key oxazolidinone **2.240** (scheme 3.1).




*Reagents and conditions*: i) $SOCl_2$, MeOH; ii) $Boc_2O$, $^{i}Pr_2(Et)N$, DCM (86%); iii) $I_2$, $PPh_3$, Imidazole, DCM, 0 $^{o}$C – rt (88%); iv) DBU, toluene, 80 $^{o}$C, (75%); v) $NaBH_4$, THF/$CH_3CN$ (85%); vi) DAST, DCM (86%).

**Scheme 3.1:** Synthesis of oxazolidinone **2.240**.

Commercially available *trans*-4-hydroxy–L-proline **2.234** was subjected to Fisher esterification[97] to yield the corresponding hydrochloride salt **2.235**. This was followed by Boc protection of the pyrrolidine nitrogen **2.235** using Boc anhydride and Hünig's base which gave the desired Boc protected ester **2.236** in 86% yield. The hydroxyl group of ester **2.236** was converted to a better leaving group.




**2.241** **2.242** **2.243**

*Reagents and conditions*: i. $(PhSe)_2$, $NaBH_4$, EtOH, Δ; ii. $H_2O_2$, pyr, DCM, -78 $^oC$ – rt. (65% over 2 steps);

**Scheme 3.2:** Synthesis of **2.243**.

Previous methods[94-96] had involved conversion of the hydroxyl group to a mesylate to form mesyloxyprolinate **2.241**. $PhSe^-$ anion was the used to displace the mesylate to give the intermediate selenide **2.242**. The selenide **2.242** was converted to the corresponding alkene **2.243** by oxidation with hydrogen peroxide followed by elimination of the resulting selenoxide, to give alkene **2.243** in 65% yield (scheme 3.2).

In order to avoid the inherent toxicity of organo-selenium compounds and to increase the yield, we developed another procedure within our group. This procedure involved replacing the hydroxyl group with iodine (as shown in scheme 3.1). The X-ray crystal structure of one of the two isomers of iodo-pyrrolidine dicarboxylate **2.237** obtained is shown below (figure 3.1). This was followed by the elimination of the iodine, using the bulky base DBU.

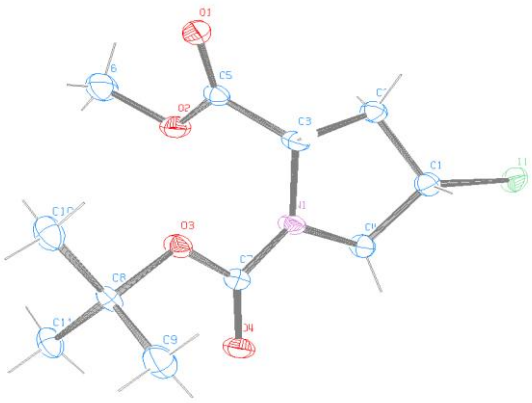
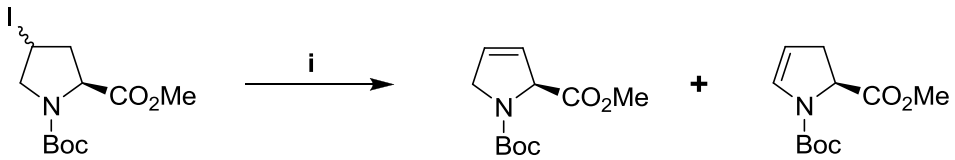


**Figure 3.1:** Crystal structure of **2.237**.

During the elimination, we obtained two separable diastereomers **2.238** and **2.244** in (9:1) ratio with the required diastereomer as the major product (scheme 3.3).



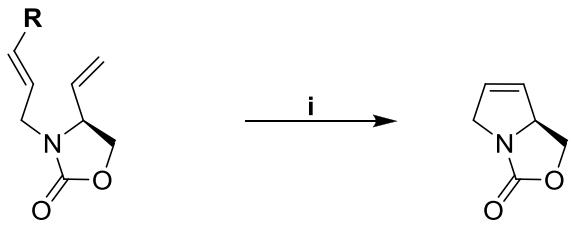

**2.237** **2.238** **2.244**

*Reagents and conditions*: i. DBU, toluene, 80 $^{o}$C, (89%) (**2.238**: **2.244** = 9:1);

**Scheme 3.3:** Formation of diasteromers **2.238** and **2.244**.

The alkene **2.238** was converted to the corresponding alcohol **2.239** using $NaBH_4$ in $THF/CH_3CN$. Although different reagents such as, DIBAL, $LiAlH_4$ could be used for the conversion of ester to alcohol,[95] $NaBH_4$ gave higher yields (scheme 3.1).

Oxazolidinone **2.240** was first formed by Pyne,[98] whose synthesis involved using a ring closing metathesis to construct the bicyclic ring system. The styrene derivative **2.246** underwent a RCM reaction, using Grubbs' 2$^{nd}$ generation catalyst to give **2.240** in an 82% yield (scheme 3.4).




**2.245, R** = H
**2.246, R** = Ph

**2.240**

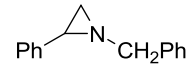
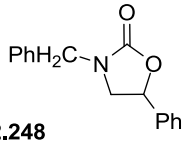
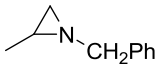
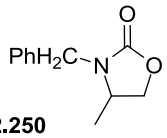
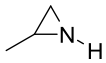
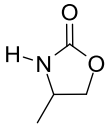
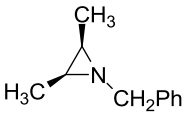
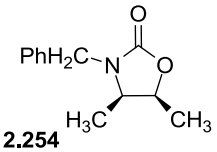
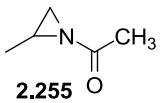
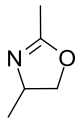
*Reagents and conditions*: i. Grubbs II, (73-82 %);

**Scheme 3.4:** Synthesis of oxazolidinone **2.240**.

The alcohol **2.239** was converted to bicyclic oxazolidinone precursor **2.240** by treatment with DAST in DCM in 86% yield using the procedure followed by Greenwood[94] (scheme 3.1).

Recently in the year 2011, Pinhas[99] and co-workers were able to perform a solvent and catalyst free conversion of an aziridine to an oxazolidinone using only carbon dioxide at low pressure and at room temperature (table 3.1).

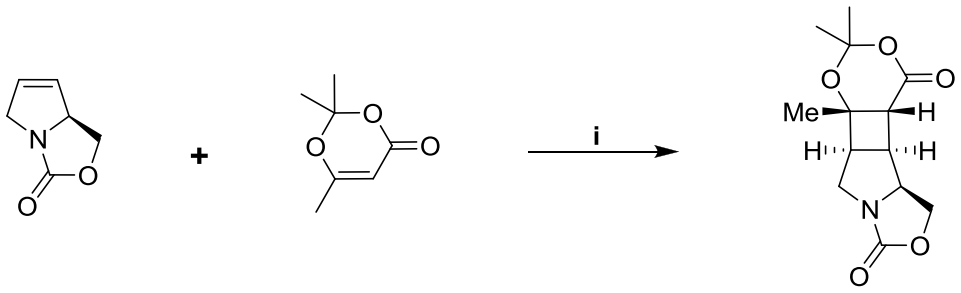
**Table 3.1** High Speed Ball Milling Reactions:

| Starting aziridine | Major product oxazolidinone | Reaction time (h) | Regioselectivity % major product |
|---|---|---|---|
|  **2.247** |  **2.248** | **17** | **100** |
|  **2.249** |  **2.250** | **17** | **93** |
|  **2.251** |  **2.252** | **17** | **100** |
|  **2.253** |  **2.254** | **17** | **100** |
|  **2.255** |  **2.256** | **17** | **100** |

When aziridine **2.249** was stirred, with no solvent or catalyst, under $CO_2$ with 3 atm pressure for 12 h, the yield of oxazolidinone **2.250** was 37%. The high speed ball milling (HSBM) method generated oxazolidinone in nearly quantitative yield with only one regioisomer. In order to decrease the time of the reactions, (HSBM) was investigated. Mechanical energy generated from HSBM has been shown to give high yields and an increase in the rate of chemical reactions, especially those reactions done without any solvent. The HSBM apparatus uses a small steel ball in a steel vial with high speed shaking to achieve small particle sizes through milling. Subsequent collisions of the milling ball with the sides of the reaction vessel provide mechanical energy to overcome the activation barrier generated in the reaction.[100,101]

### 3.1.1.2 Diastereofacial selectivity of the oxazolidinone precursor 2.240.

Greenwood was the first to discover that reactions on the double bond of oxazolidinone **2.240** occurred in a diastereoselective fashion.[102,103] For instance it was found that irradiation of oxazolidinone **2.240** with dioxane **2.257** resulted in a cyclobutane photoadduct **2.258** with complete regio- and stereoselectivity together in 38% plus unreacted starting materials(scheme 3.6). The photocycloaddition occurred only on the more sterically congested concave face of oxazolidinone **2.240**.

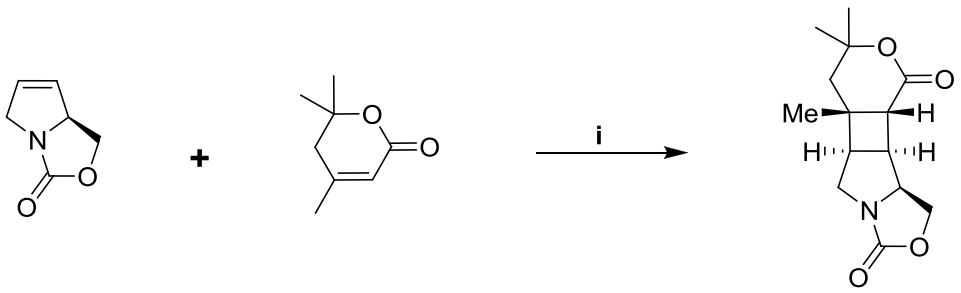



**2.240** **2.257** **2.258**

*Reagents and conditions*: i. *hv*, EtOAc (38%);

**Scheme 3.6:** Formation of cyclobutane photoadduct **2.258**.

Similar control of the stereochemistry was also observed by Greenwood using pyranone **2.259,** which on irradiation with oxazolidinone **2.240** gave the photoadduct **2.260** (scheme 3.7).[102,103]

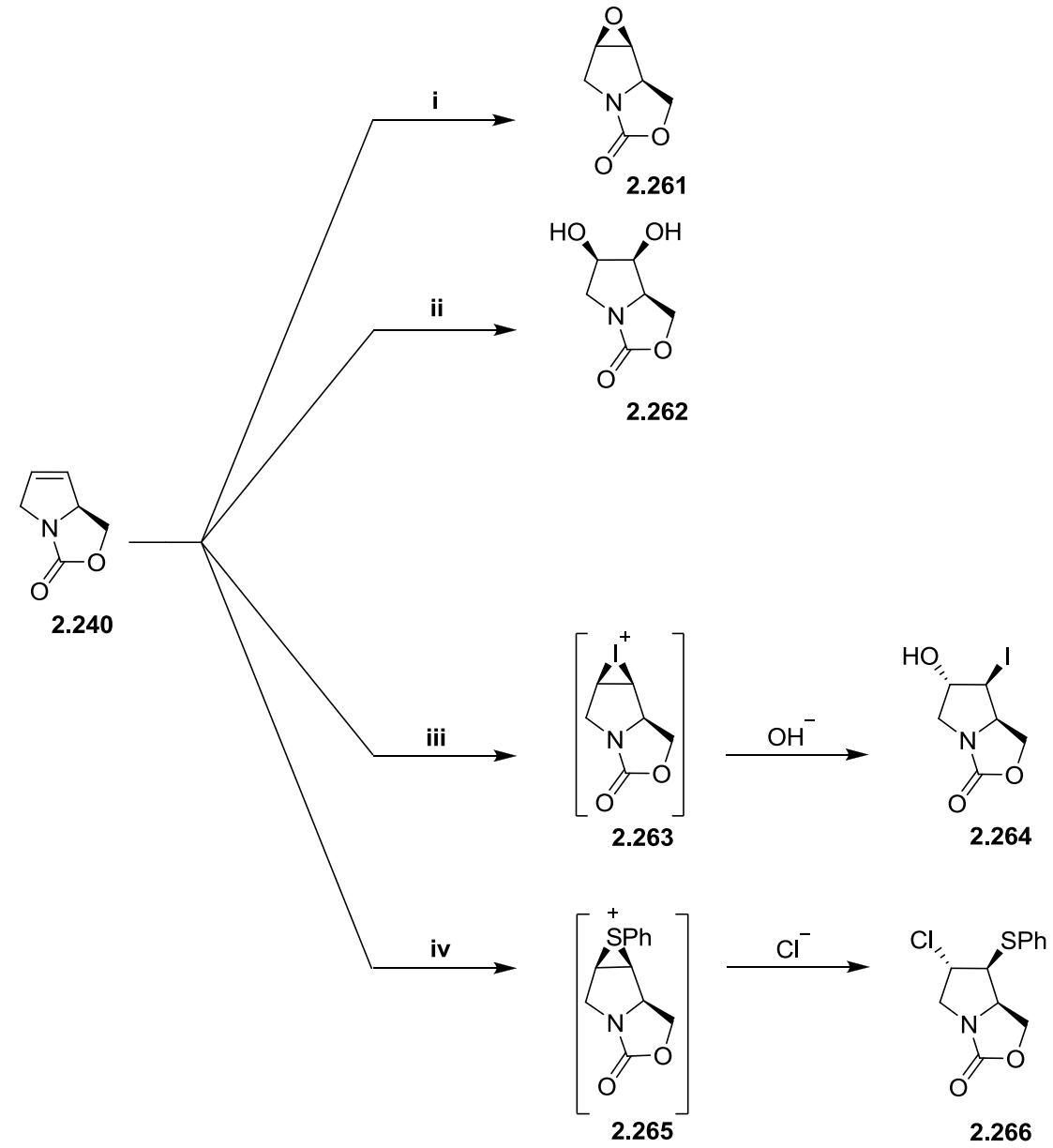



**2.240** **2.259** **2.260**

*Reagents and conditions*: i. *hv*, EtOAc (43%);

**Scheme 3.7**

Following on from these photochemical reactions, Greenwood and Adrian Murray discovered the same stereoselectivity occurred when oxazolidinone **2.240** was treated with a series of electrophiles (scheme 3.8).[103]

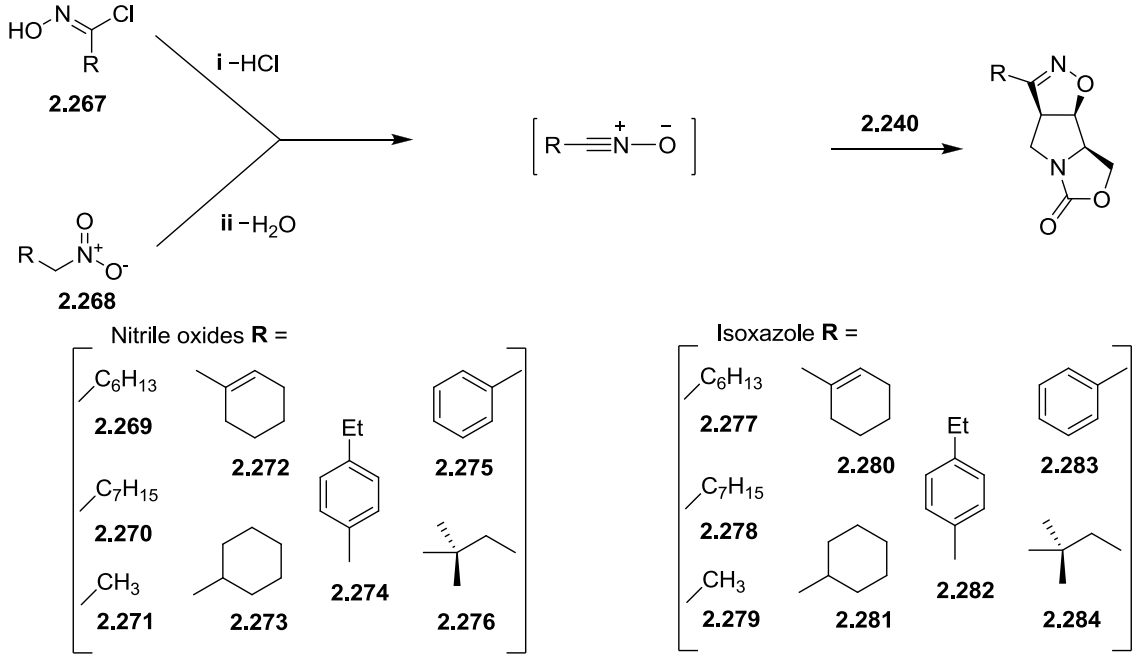



*Reagents and conditions* i) *m*-CPBA (33%) OR DMDO (80%); ii) $OsO_4$ (83%); iii) NIS (60%); iv) PhSCl (65%);

**Scheme 3.8**

As shown in the (scheme 3.8), electrophilic addition to oxazolidinone **2.240** was exclusively directed onto the *endo* face as expected.[103] Additional examples of regiocontrol were then shown by Greenwood in the formation of compounds **2.264** and **2.266**.[102,103] The nucleophilic attack of hydroxide and chloride on activated iodonium **2.263** and sulphonium **2.265** intermediates was shown to occur at the least hindered carbon.

Further investigations by Jason Lai,[96] involved an intermolecular 1,3-dipolar cycloaddition. Treating oxazolidinone **2.240** with a series of nitrile oxides **(2.269-2.276)**, which act as the electrophiles, gave a range of tricyclic isoxazoles **(2.277-2.284)**. Nitrile oxides were generated *in situ* in these cycloadditions in the presence of $Et_3N$ (scheme 3.9).




*Reagents and conditions*: i. **2.240**, $Et_3N$, $C_6H_6$, rt; ii. **2.240**, PhNCO or TsCl, $Et_3N$, $C_6H_6$, rt;

**Scheme 3.9**

An explaination for the diastereoselectivity (scheme 3.9) was believed to be due to the distribution of electron density within the alkene **2.240**. An investigation was carried out within the Parsons group by Eddy Viseux, which gave a quantitative theoretical explanation of the origin of disastereofacial selectivity for both the electrophilic dihydroxylation and epoxidation of alkene **2.240**.[103] Using *ab initio* calculations at the 6-31G* level, the molecular orbitals of the most stable conformation of oxazolidinone **2.240** were calculated (using the $MM^+$ set).

As shown in figure 3.2 the model calculated by Eddy Viseux suggested that:

1. There was a distortion in the HOMO that led to greater electron density being placed on the *endo* face of the compound. This may explain the observed diastereofacial selectivity of the electrophilic attack.

2. The nitrogen lone pair appears not to be in conjugation with the carbonyl system. Further evidence for this was provided by the IR stretch frequency for the C=O at 1751 $cm^{-1}$. This is higher than the range usually expected for such a carbamate system.

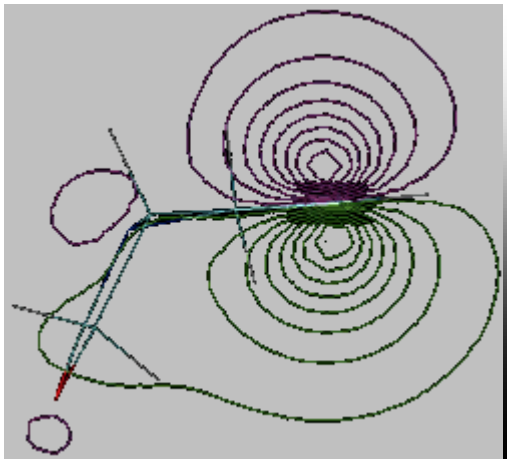


**Figure 3.2:** 6-31-G* representation of the HOMO of oxazolidinone **2.240**.[103]

Pyne[98] also observed the same diastereofacial selectivity when dihydroxylating oxazolidinone **2.240** with osmium tetroxide. However they concluded that the stereochemical outcome was due to the pseudo-axial protons H-10 and H-12, which cause the *exo* face of oxazolidinone **2.240** to be more sterically hindered for the electrophilic attack (figure 3.3).

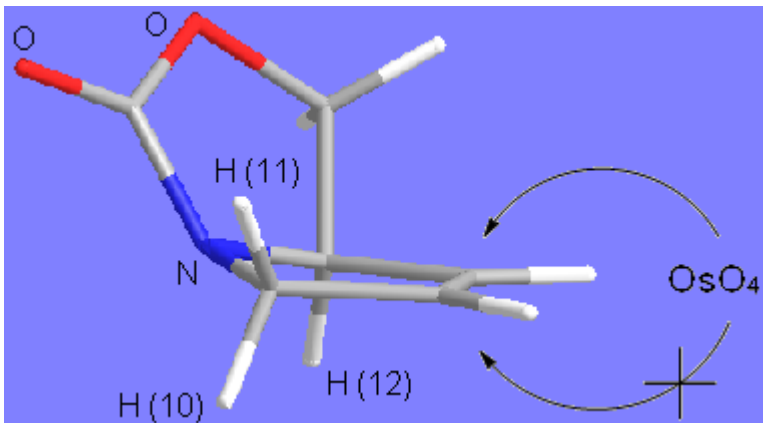
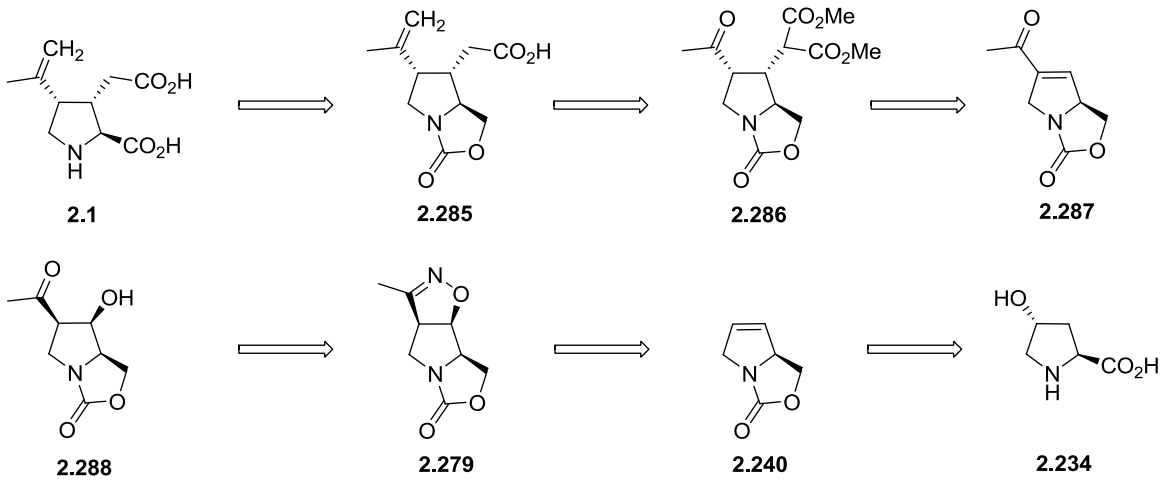



**Figure 3.3:** Stereochemical model (Spartan AM1) of oxazolidinone **2.240**.[98]

## 3.2. Studies towards the synthesis of kainic acid 2.1.

### 3.2.1. Retrosynthesis of kainic acid 2.1:

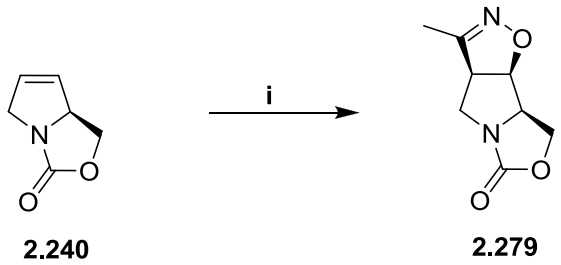
For the total synthesis of kainic acid **2.1**, we devised a route starting from a cheap and readily available starting material *trans*-4-hydroxy-L-proline **2.234** (scheme 3.10). This would be then transformed into the key oxazolidinone **2.240**, where the stereochemistry at C-2 is fixed into one correct position for kainic acid **2.1**. Oxazolidinone **2.240** would be then subjected to 1,3-dipolar cycloaddition with ethyl nitrile oxide in the presence of TsCl and $Et_3N$ to give the tricyclic isoxazole **2.279**. Reduction of **2.279** by treatment with Raney Ni under $H_2$ atmosphere with MeOH as solvent would give $\beta$-hydroxy ketone **2.288**. The resulting ketone **2.288** on dehydration using *p*-TSA would give enone **2.287**. The enone **2.287** would be then transformed into the key dicarboxylate **2.286** by 1,4 addition, where the stereochemistry of C-3 and C-4 is fixed into the correct position for kainic acid **2.1**. The dicarboxylate **2.286** would further undergo Wittig reaction followed by decarboxylation to give bicyclic acid **2.285**. The compound **2.285** would be then transformed into kainic acid **2.1** according to the procedure devised by Parsons.[93]




**Scheme 3.10:** Retrosynthesis of kainic acid **2.1.**

### 3.2.2. 1,3-Dipolar cycloaddition of oxazolidinone 2.240.

Oxazolidinone **2.240** was prepared by the modified procedure of Jason Lai[96] (scheme 3.11). The oxazolidinone **2.240** was subjected to 1,3-dipolar cycloaddition using a nitrile oxide electrophile generated *in situ*. Triethylamine was added to a solution of oxazolidinone **2.240** and nitroethane in the presence of TsCl which gave only one diastereoselective product, a tricyclic isoxazole **2.279** in 68% yield. The structure of the resulted adduct was confirmed with X-ray crystallographic analysis by Jason Lai[96] (figure 3.4).




*Reagents and conditions*: i. $EtNO_2$, TsCl, $Et_3N$, benzene, 12 h, 68%;

**Scheme 3.11:** Synthesis of tricyclic isoxazole **2.279**.

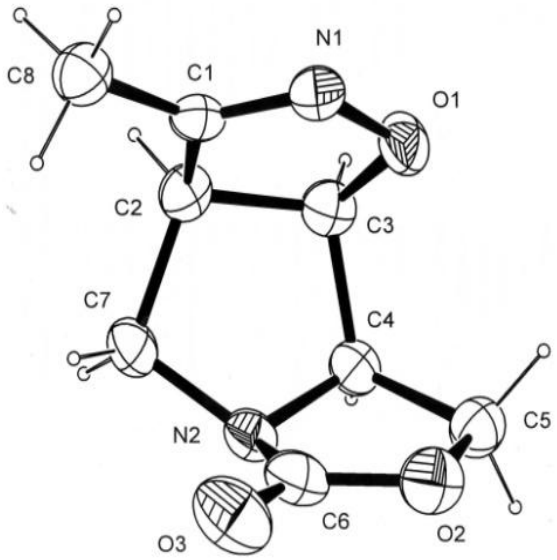
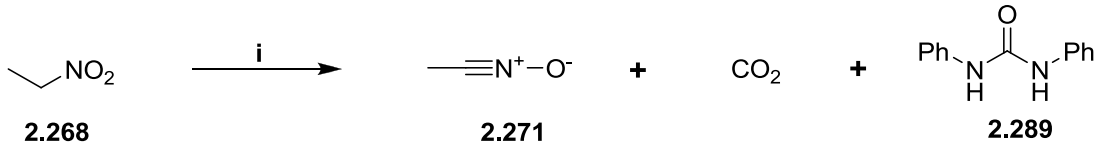



**Figure 3.4:** X-ray crystallographic structure of **2.279**.

Previous attempts by Jason Lai[96] to form tricyclic isoxazole **2.279** involve generation of ethyl nitrile oxide **2.271** *in situ* by a procedure developed by Mukaiyama and Hoshino.[104] In that procedure, nitroethane was dehydrated with phenyl isocyanate in the

presence of triethylamine, to generate the desired ethyl nitrile oxide **2.271**. However, in this 1,3-dipolar cycloaddition, diphenyl urea **2.289** was precipitated as a by-product in the solution, which is difficult to separate from the desired tricyclic isoxazole **2.279** even by flash chromatography due to similar solubilities[96] (scheme 3.12) .




**2.268** **2.271** **2.289**

*Reagents and conditions*: i. PhNCO, $Et_3N$, Δ, $C_6H_6$;

**Scheme 3.12**

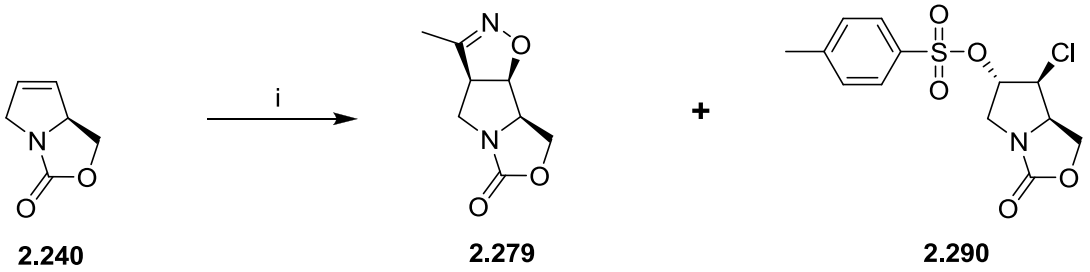
In order to improve the yield and replace the potentially carcinogenic benzene as solvent, we repeated the same reaction using a variety of common alternatives (table 3.2). In each case the reaction never went to completion, and the yield was lower compared to the use of benzene as solvent. Hünig's base was used in place of triethylamine but this only resulted in a lowering of the yield of isoxazole **2.279**. Although we tried to increase the time of the reaction from 12 hrs to 7 days under the same conditions, we could not manage to get the completion of reaction, and the yield was low. We continued with benzene as solvent which gave the maximum yield.

**Table 3.2:** Formation of tricyclic isoxazole **2.279**.

| S.No | Reagents and Conditions (i) | Solvent | Yield (%)* |
|---|---|---|---|
| 1 | **2.240**, $EtNO_2$, $Et_3N$, TsCl, 0 $^oC$ - rt, 7 days. | $C_6H_6$ | 68 |
| 2 | Same as above | Toluene | 55 |
| 3 | Same as above | THF | 50 |
| 4 | Same as above | DCM | 58 + 15 (**2.290**) |
| 5 | Same as above | $CH_3CN$ | 62 |
| 6 | Same as above | $Et_2O$ | 45 |
| 7 | **2.240**, $EtNO_2$, Hünig's base, TsCl, 0 $^oC$ - rt, 12 h. | $C_6H_6$ | 60 |

* = In each case starting material was also recovered.

When DCM was used as a replacement solvent to prepare tricyclic isoxazole **2.279**, we observed something unconventional compared to scheme 3.11. We obtained an unusual byproduct **2.290** (scheme 3.13). The byproduct **2.290** was stable and could be isolated by flash column chromatography to give a crystalline solid. When analysed by X-ray crystallography, we discovered this to be the oxysulfonyl chloride compound **2.290** as shown below (figure 3.5) which in turn reduces the yield of the reaction. The byproduct **2.290** could be avoided by using benzene as solvent. Interestingly this byproduct **2.290** was not seen in any other reaction using alternative solvents (table 3.2).




*Reagents and conditions*: i. $EtNO_2$, TsCl, $Et_3N$, DCM, 12 h.

**Scheme 3.13**

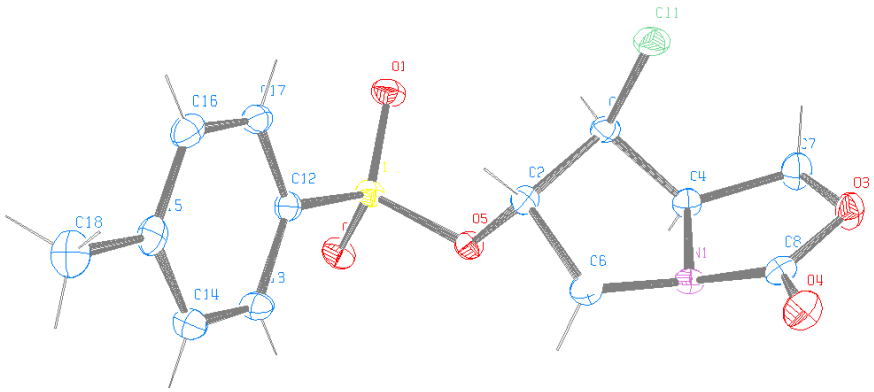
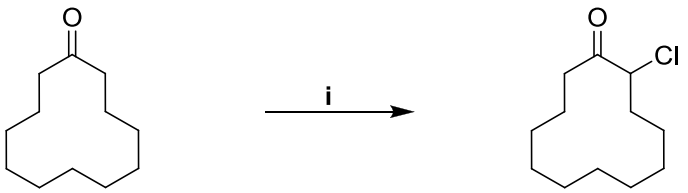



**Figure 3.5:** X-ray crystallographic structure of **2.290**.

An explanation for this result could be, TsCl acting as a chlorinating agent in presence of DCM and oxazolidinone **2.240**.



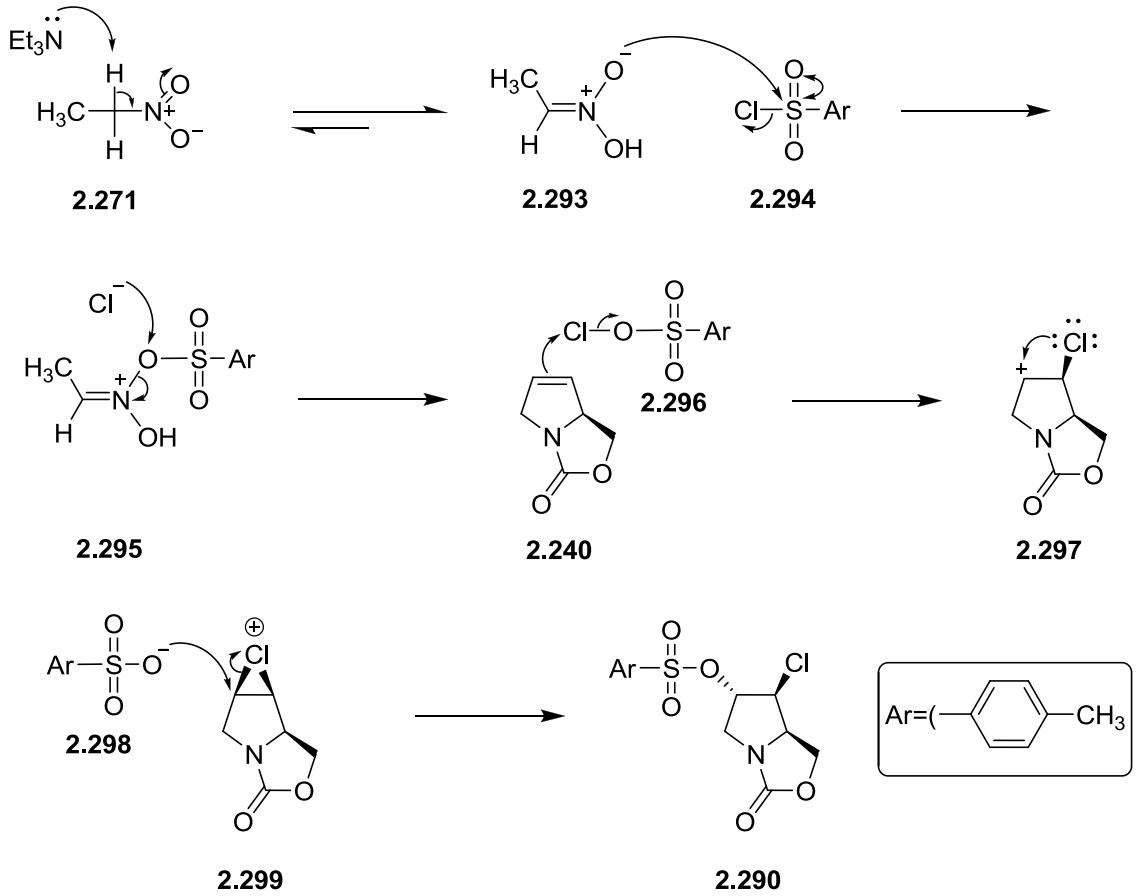

**2.291** **2.292**

*Reagents and conditions*: i. LDA, TsCl, THF, 83%;

**Scheme 3.14**

Brummond[105] described α-chlorination of ketones using TsCl, in which α-chloroketones are formed in good yield. Thus, inferring TsCl is chlorinating agent. The ketone **2.291** on treatment with TsCl in presence of LDA gave chlorinated ketone **2.292** in 83% yield (scheme 3.14).

The plausible mechanism for the formation of byproduct **2.290** is show below (scheme 3.15).

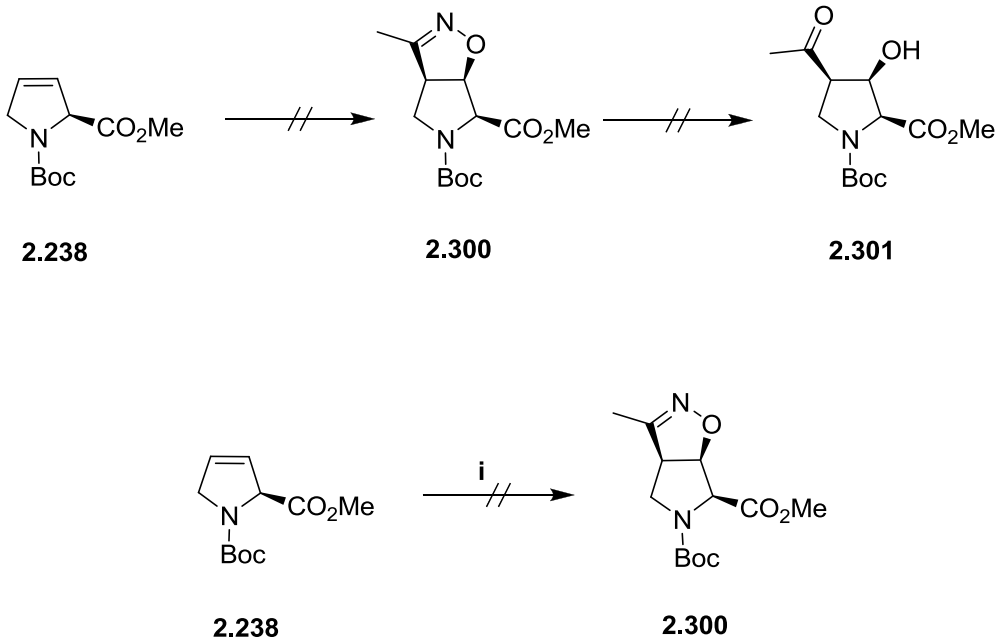



**Scheme 3.15**

Triethylamine reacts with nitroethane **2.271** to give the nitronic acid **2.293**, which reacts with TsCl **2.294** to give the nitroxy-sulfonyl compound **2.295**. Chloride ion reacts with **2.295** to give oxy-sulfonyl chloride **2.296**. Oxazolidinone **2.240** reacts with **2.296** to give positively charged oxazolidinone chloride **2.297** and aromatic anion **2.298**. The anion attacks the compound **2.299** from the least hindered side, to give the more stable novel aromatic oxy-sulfonyl chloride **2.290**. Consequently, we proved that the oxazolidinone **2.240** ring plays a pivotal role in the formation of tricyclic isoxazole **2.27** (scheme 3.11-3.15).

### 3.2.3. Attempted formation of bicyclic isoxazole

Subsequently upon the preparation of tricyclic isoxazole **2.279**, we envisaged another route which could have potentially avoided de-protection in later steps (scheme 3.16).

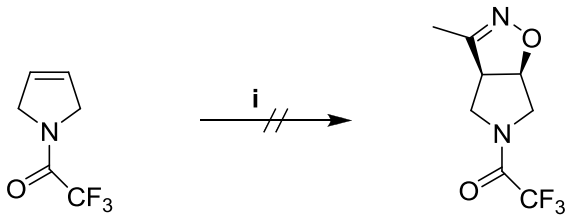



*Reagents and conditions*: i. $EtNO_2$, TsCl, $Et_3N$, DCM, 12 h;

**Scheme 3.16**

A failed attempt to use the similar conditions (scheme 3.11) on the double bond of the Boc-protected ester **2.238** to get bicyclic isoxazole **2.300**, which could have reduced further steps in opening of the oxazolidinone ring **2.240**. Unfortunately we only recovered the starting material **2.238** (scheme 3.16).

In order to mimic the reaction conditions used in scheme 3.11 on the double bond of trifluoro compound **2.302**, we tried to obtain **2.303**. We failed to get the desired product **2.303** and instead we recovered the starting material (scheme 3.17).




**2.302** **2.303**

*Reagents and conditions*: i. $EtNO_2$, *p*-TsCl, $Et_3N$, DCM, 12 h;

**Scheme 3.17**

### 3.2.4. Reduction of isoxazole ring:

The isoxazole ring is a biologically important entity which is a component of some of the nucleoside analogs.[106] The isoxazole structure is found in some pharmacologically interesting natural products, for example, cycloserine[107] **2.304** and acivicin[108] **2.305** (figure 3.6). Cycloserine **2.304** is an antibiotic used in the treatment of tuberculosis,[109] effective against *Mycobacterium tuberculosis*.[110] Acivicin **2.305** is used as an antineoplastic agent, which acts as a glutamine analog antimetabolite.

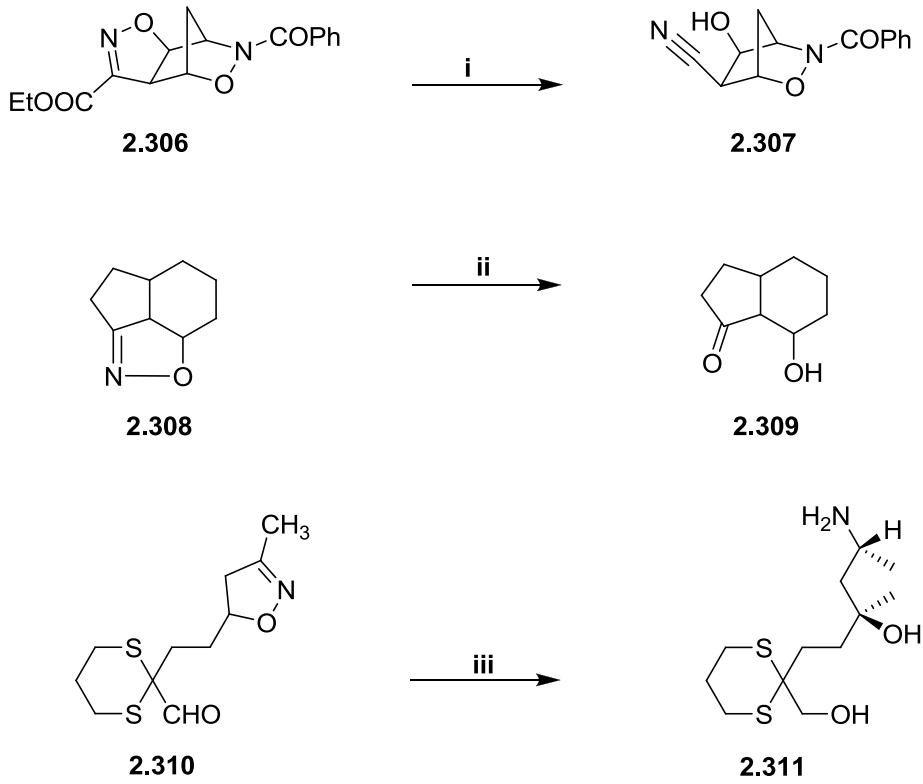

**2.304** **2.305**

Cycloserine Acivicin

**Figure 3.6:** Structure of cycloserine **2.304** and acivicin **2.305**

There are a variety of methods for the transformations of isoxazolines into other useful functionality[111-114]. For instance, dehydrogenation of intermediate iminoalcohol arising from N-O bond cleavage of **2.306** affords *β*-hydroxy nitriles **2.307**. The N-O bond cleavage of **2.308** followed by hydrolytic workup provides *β*-hydroxyketone **2.309**.

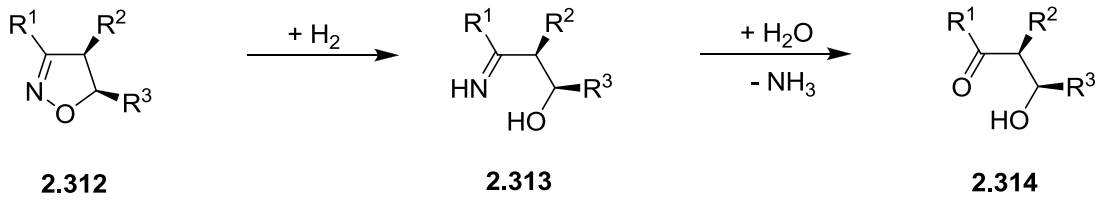
Complete reduction of the isoxazoline ring **2.310** provides $\gamma$-aminoalcohols **2.311** (scheme 3.18).




*Reagents and conditions*: i. $Na_2CO_3$, MeOH, rt, 12 h, 66%; ii. (a) $H_2$, Raney Ni, HOAc. (b) $NaHCO_3$, $H_2O$; iii. (a) DIBAL. (b) Resolution;

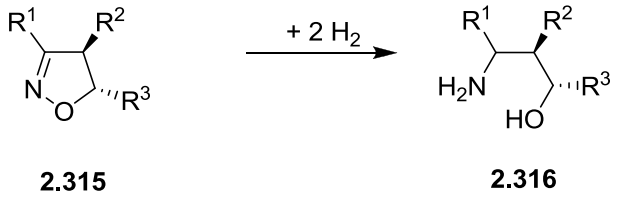
**Scheme 3.18**

According to literature[115] the most popular methods for reduction of isoxazoline **2.312** is hydrogenation with Raney Ni[116] or Pd/C[117] in the presence of boric acid in methanol/water at room temperature leads to $\beta$-hydroxy ketones **2.314** (scheme 3.19). The stereochemistry of the reactant **2.312** is retained in the product **2.314**.




**Scheme 3.19**

Reaction of 4,5-Dihydroisoxazoles **2.315** with sodium metal in ethanol or by $NaBH_4$ and $NiCl_2 \cdot (H_2O)_6$ in methanol at -30 $^oC$ yield *β*-amino alcohols **2.316** (scheme 3.20).[118]

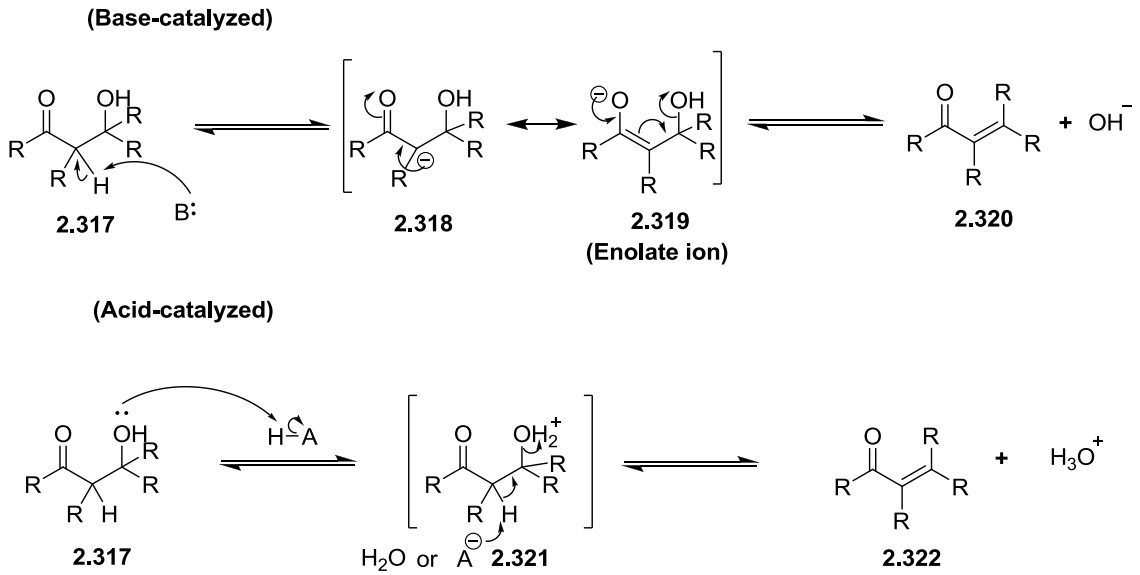



**2.315** **2.316**

**Scheme 3.20**

### 3.2.5. Dehydration of the *β*-hydroxy ketone using *p*-TSA.

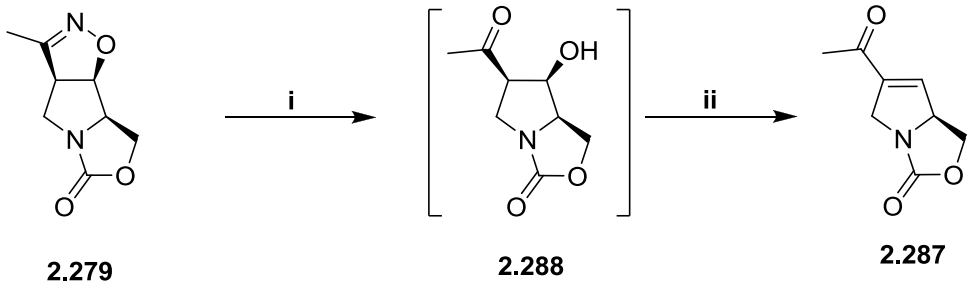
Dehydration of a *β*-hydroxy ketone can be done by both base catalysed or acid catalysed method. The mechanism can be seen below (scheme 3.21).




**Scheme 3.21**

### 3.2.6. Formation of enone 2.287

Returning to tricyclic isoxazole **2.279** the reduction was conducted using Raney Ni in the presence of boric acid in methanol/water at room temperature. We hoped to obtain the *β*-hydroxy ketone **2.288** (scheme 3.22). However, *β*-hydroxy ketone **2.288** was difficult to isolate and underwent dehydration using a catalytic amount of *p*-TSA·$H_2O$ in toluene using Dean-Stark apparatus[119] to give enone **2.287** in 89% yield (starting from **2.279**) (scheme 3.22). The resulting enone **2.287** was confirmed by X-ray crystallographic analysis (figure 3.7). *β*-Hydroxy ketone **2.288** was isolated by Jason Lai[96], although the yield of enone was very low, but we found it difficult to isolate and yield of enone was improved to a large extent.




*Reagents and conditions*: i. Raney Ni, $H_2$, Boric Acid, Methanol/Water (5:1), rt; ii. *p*-TSA·$H_2O$, Toluene, reflux (80$^oC$), 89% overall yield;

**Scheme 3.22:** Synthesis of enone **2.287**.

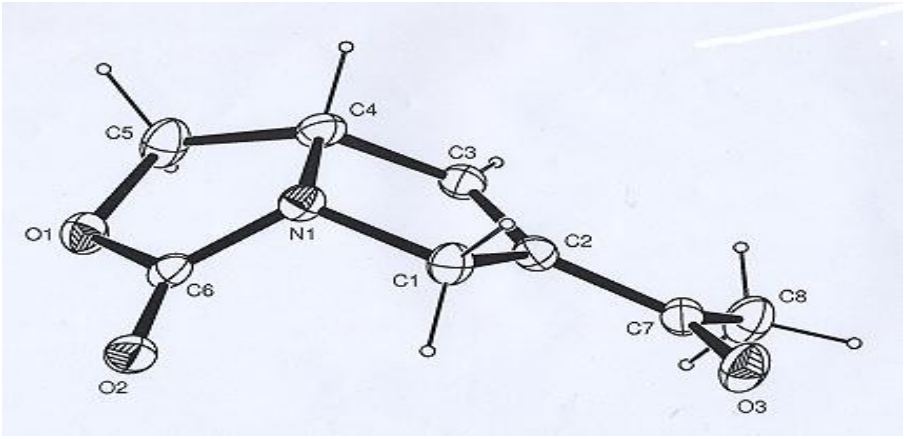



Figure A of **2.287.**

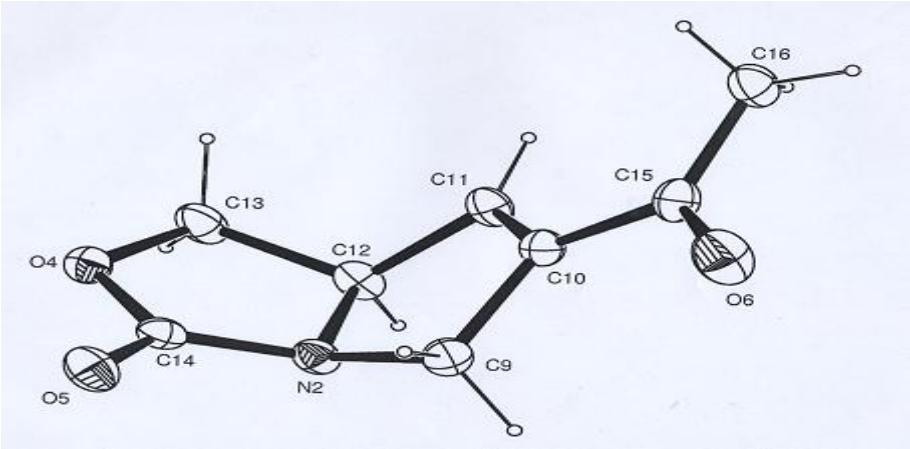


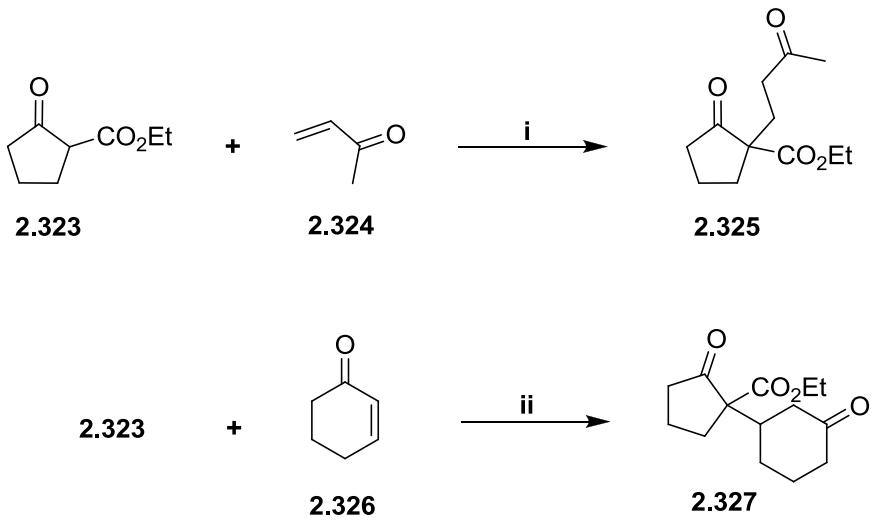

Figure B of **2.287.**

**Figure 3.7 :** X-ray crystallographic structure of **2.287**.

### 3.2.7. Michael addition reaction.

Michael reaction[120,121] is an important carbon-carbon bond-forming reaction. In classical example of Michael reaction, the reaction is between Michael donor (usually diethyl malonate) and Michael acceptor. The enone **2.287** acts as a good Michael acceptor. The nucleophilic conjugate addition occurs usually with *α,β*-unsaturated carbonyl compounds, and such nucleophilic addition are called as nucleophilic conjugate addition or 1,4-nucleophilic addition. An example of highly efficient C-C bond-forming reactions in aqueous media catalysed by monomeric vanadate species is reported by Kaneda[122] (scheme 3.23). Here the substrate **2.323** reacts with enones **2.324** and **2.326**

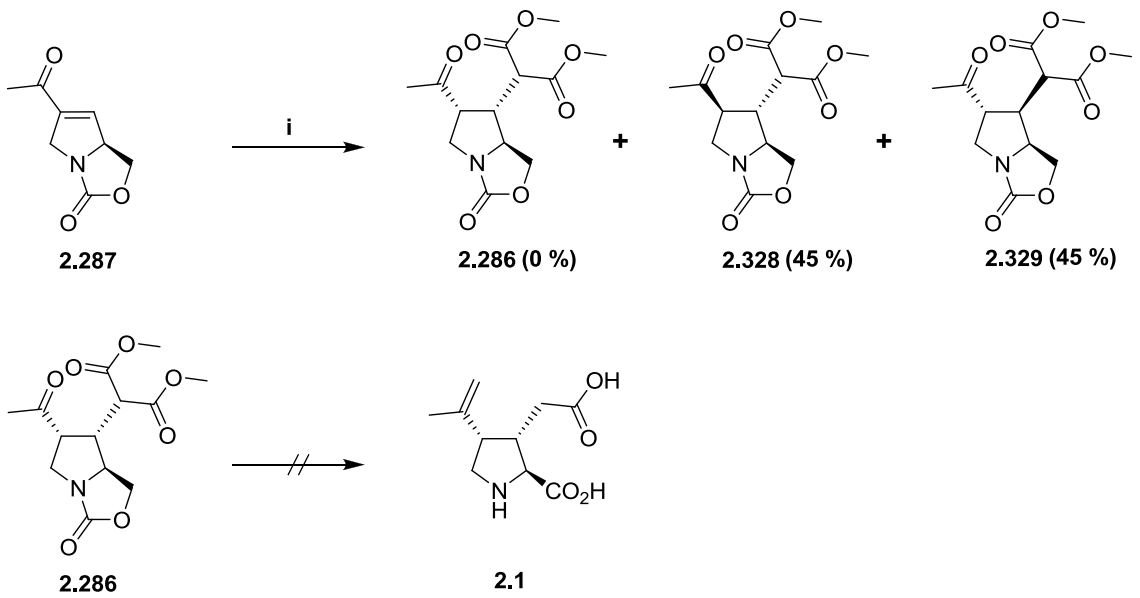
in presence of catalyst VAp and VAp-hw to give esters **2.325** and **2.327** respectively in high yields.[122]




*Reagents and conditions*: i. VAp (0.008 g), $H_2O$ (50 mL), 40 $^oC$, 1.5 h, 92%; ii. VAp-hw, $H_2O$ (3 mL), 50 $^oC$, 0.5 h, 99%;

**Scheme 3.23**

The enone in compound **2.287** should undergo 1,4-nucleophilic addition in a similar fashion to the (scheme 3.23) as above. The proposed Michael reaction for enone **287**, can be seen below (scheme 3.24).




*Reagents and conditions* i: NaH, THF, dimethyl malonate, 0 $^oC$ – rt, 90%, (**2.328**:**2.329** = 1:1);

**Scheme 3.24:** Michael reaction of enone **2.287**.

We expected to get the diester **2.286**, which could have formed the key intermediate for the total synthesis of kainic acid **2.1** (scheme 3.24). This diester **2.286** has the same stereochemistry as in kainic acid **2.1**. On Michael reaction of enone **2.287** with the carbanion derived from dimethyl malonate, we isolated two diastereomers **2.328** and **2.329** in 1:1 ratio (scheme 3.24). The overall yield of the reaction was 90%. Both the diastereomers **2.328** and **2.329** were solids, but we could only obtain X-ray quality crystals of **2.329**, by means of which we could determine the exact structure of the compound **2.329** (figure 3.8). In (scheme 3.24) it is clear that the nucleophile can attack from either side of the enone **2.287** and due to the bulk, the *anti* stereochemistry is formed.

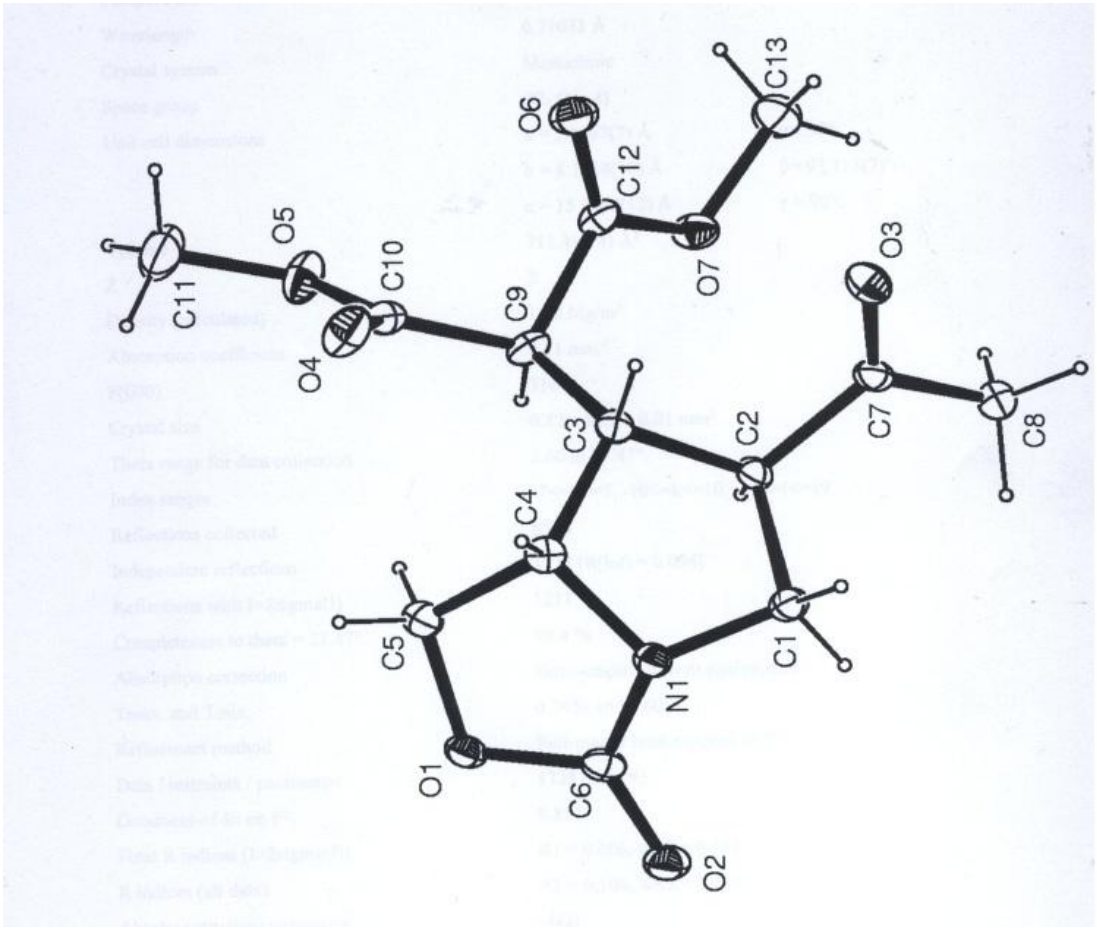
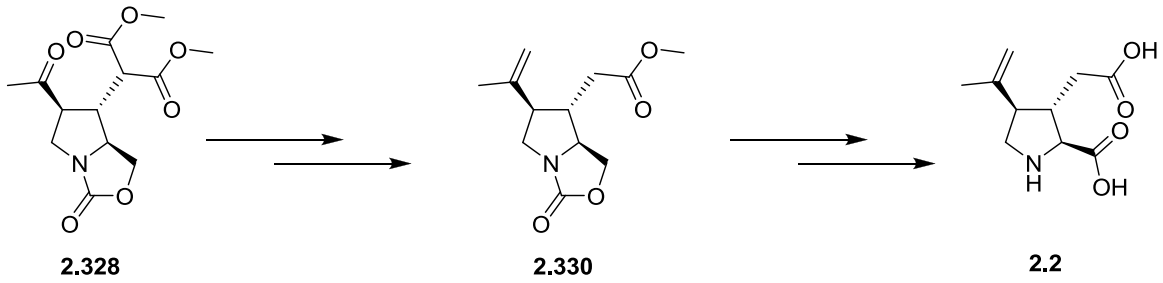



**Figure 3.8:** X-ray crystallographic structure of **2.329**.

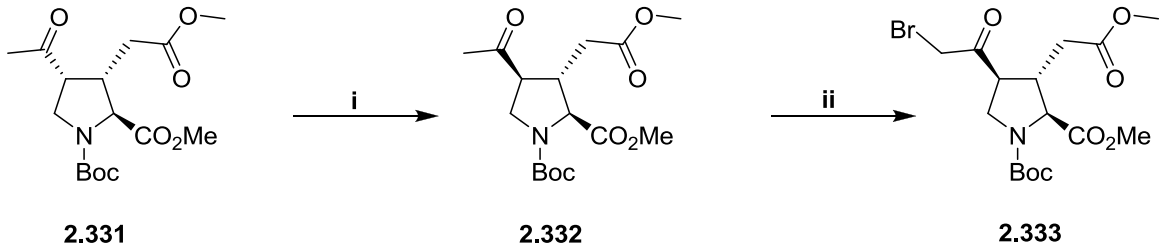
We attempted to utilise compounds **2.328** and **2.329** to further investigate the total synthesis of the kainates. The diester **2.328** has the required stereochemistry for the total synthesis of allokainic acid **2.2** (scheme 3.25 shown below).




**Scheme 3.25**

### 3.2.8. Epimerisation of C-4 group.

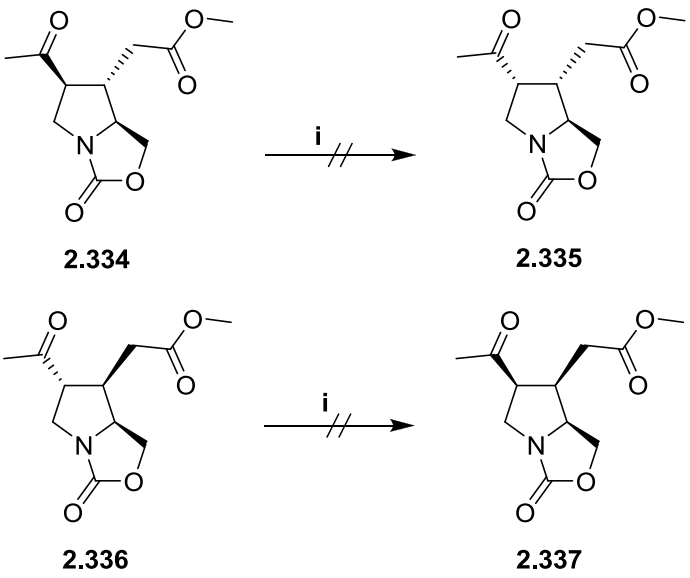
Jack E. Baldwin[123] in the synthesis of heteroaromatic acromelic acid analogues from kainic acid **2.1** used DBU to epimerise the C-4 position of **2.331** (scheme 3.26).




*Reagents and conditions* i: DBU, Toluene, rt; ii: LiHMDS, TMSCl, –78 $^{o}$C, then $PhN^{+}Me_3Br_3^{-}$;

**Scheme 3.26**

We desired to use the same method used by Baldwin, for the epimerisation of the diastereomers **2.328** and **2.329** in order to obtain isomers with the same *cis*-stereochemistry (scheme 3.27).




**2.334** **2.335**

**2.336** **2.337**

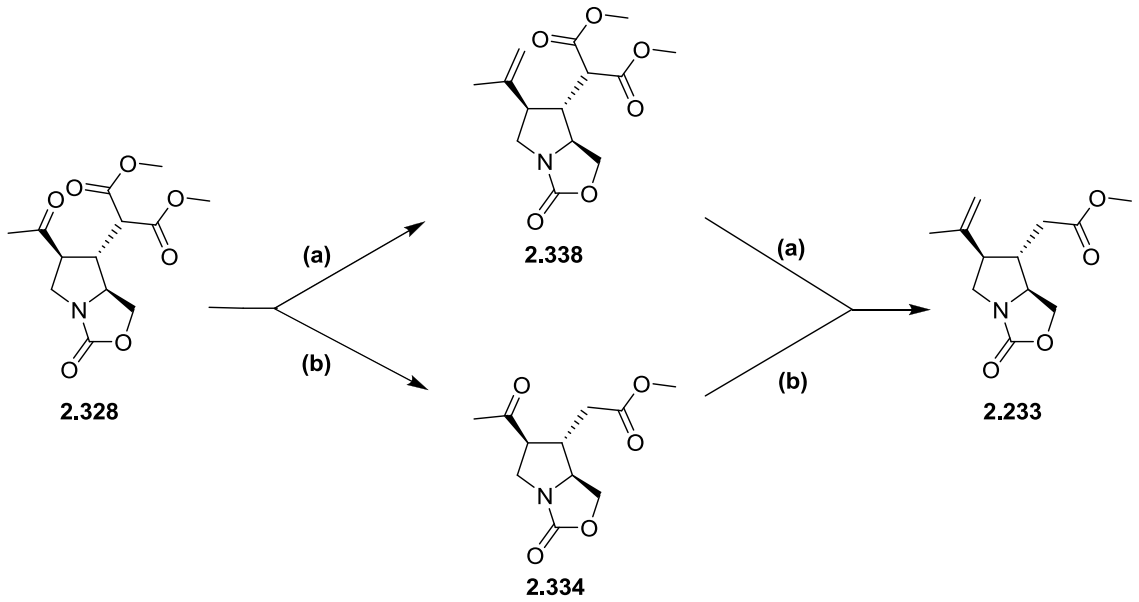
*Reagents and conditions*: i. DBU, toluene, rt;

**Scheme 3.27**

# 3.3. Studies towards the formal synthesis of allokainic acid 2.2.

### 3.3.1. Decarboxylation of diastereomers 2.328 and 2.329.

There are two possible routes for the conversion of diester **2.328** into acetate **2.233** (scheme 3.28). In route **(a)**, the diester **2.328** undergoes a Wittig reaction to convert into alkene **2.338** and then a further Krapcho decarboxylation[124] to give acetate **2.233**. In route **(b)** the diester **2.328** undergoes Krapcho decarboxylation first, followed by Wittig reaction to give acetate **2.233**.

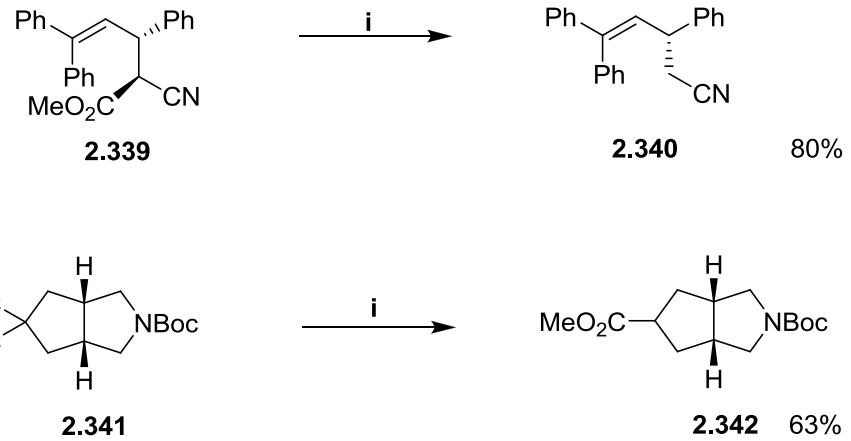



**Scheme 3.28**

We started with route **(b)** (scheme 3.28), as the ester **2.334** could be used for the epimerization of the C-2 group (scheme 3.27). In the route **(b)** Krapcho decarboxylation is followed by Wittig reaction.

### 3.3.1.1. Krapcho decarboxylations:

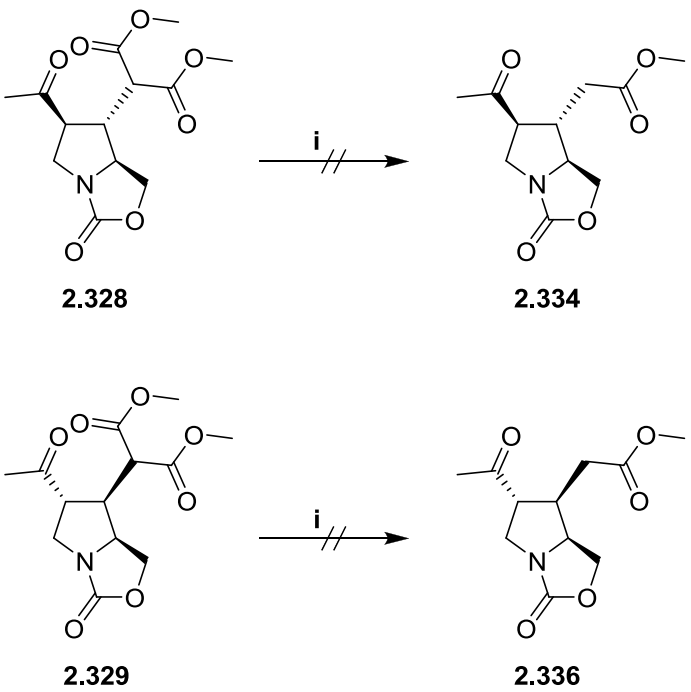
Paul Krapcho studied the synthetic applications and mechanism of the decarboxylations of geminal diesters and related systems in DMSO by water and /or by water with added salts.[124] Most of the protecting groups in the substrate are tolerated under the reaction conditions, with the stereochemistry retained. Some examples can be seen in (scheme 3.29). The compound **2.339** undergoes Krapcho decarboxylation using NaCl in presence of DMSO to give exclusively **2.340** in 80% yield. The diester **2.341** undergoes decarboxylation using NaCN in presence of DMSO to give the bicyclic ester **2.342** in 63% yield. We preferred NaCl over NaCN as the yields were high (scheme 3.29).




*Reagents and conditions*: i. NaCl, DMSO, 160 $^{o}$C; ii. NaCN, DMSO, 160 $^{o}$C;

**Scheme 3.29**

The decarboxylation was tried on the diesters **2.328** and **2.329** (formed in scheme 3.24). There was no desired product formed and the starting material was decomposed without any isolated products (scheme 3.30).



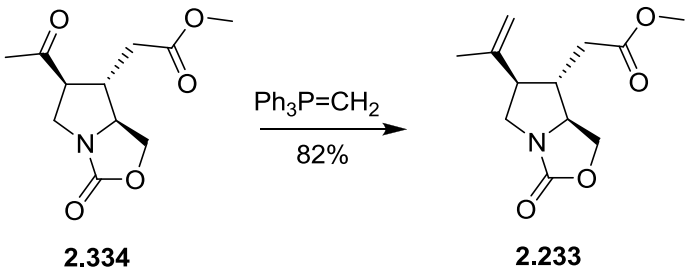

*Reagents and conditions*: i. NaCl, DMSO/$H_2O$, 170 $^{o}$C, 0% (starting material decomposed);

**Scheme 3.30**

We decided to attempt the alternative route **(a)** (scheme 3.28), and apply Wittig conditions on the diesters **2.328** and **2.329** to convert the ketone group to alkene group.

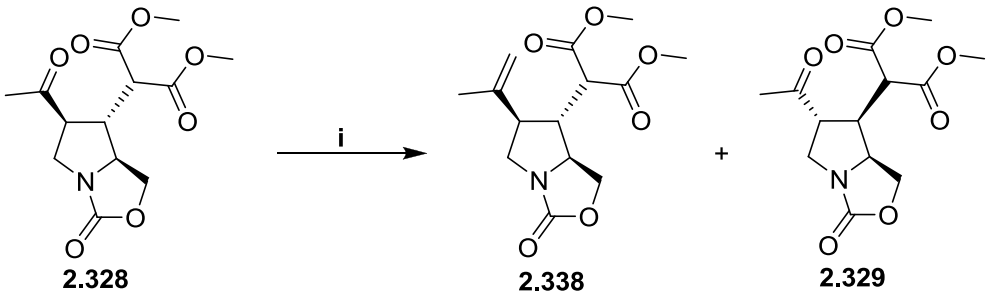
### 3.3.2. Wittig reactions.

Wittig[125-127] reactions are the most commonly used reactions in organic synthesis for the conversion of a keto group to alkene. For the Wittig reaction, we used the conditions used by Stephen Hanessian[48] in the stereoselective synthesis of kainic acid **2.1** and allokainic acid **2.2** (scheme 3.31).




**Scheme 3.31:** Hanessian's Wittig reaction.

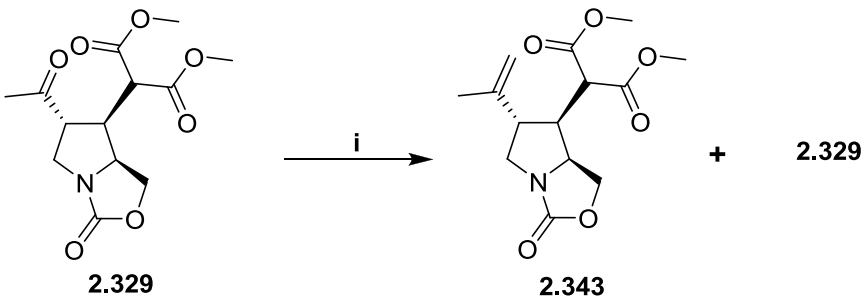
We observed some noteworthy results shown below (scheme 3.32). We started with compound **2.328** which in subsequent steps could give allokainic acid **2.2**. Here we got the desired alkene **2.338** in 72% yield and there was a remarkable change in stereochemistry of the starting material **2.328** which gave the opposite diastereomer **2.329** in 10% yield as a by-product.




*Reagents and conditions*: i. *n*-BuLi (2.5M), -78 $^{o}$C, $Ph_3PMeBr$/THF, (**2.338** =72%), (**2.329** = 10%);

**Scheme 3.32**

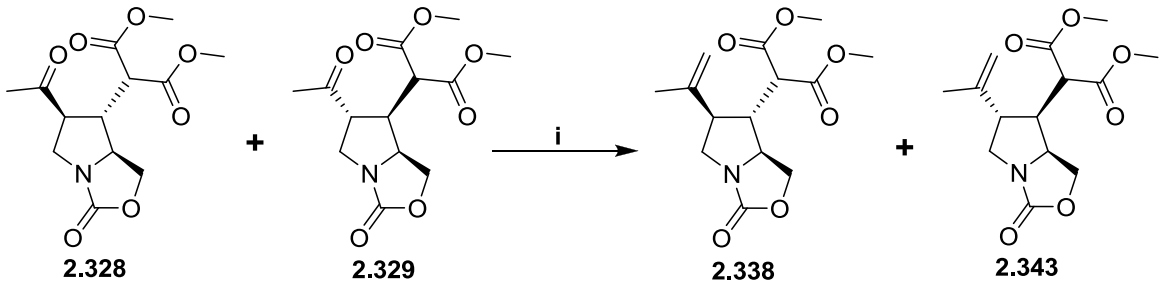
Then we tried the Wittig reaction using similar conditions used above (scheme 3.32) for the other diastereomer **2.329**. Here we got the alkene **2.343** in 81% yield and there was some starting material recovered (scheme 3.33). Here we could not observe any change in stereochemistry.




*Reagents and conditions*: i. *n*-BuLi (2.5M), –78 $^{o}$C, $Ph_3PMeBr$/THF, 81%;

**Scheme 3.33**

At this point, we tried Wittig reaction on the mixture of both the diastereomers **2.328** and **2.329** and here we got the alkenes **2.338** and **2.343** in 77% overall yield, with the later **2.343** as the major product (scheme 3.34). The alkenes **2.338** and **2.343** were difficult to separate when combined together.




*Reagents and conditions*: i. *n*-BuLi (2.5M), –78 $^{o}$C, $Ph_3PMeBr$/THF, overall 77%, **2.343** (major product);

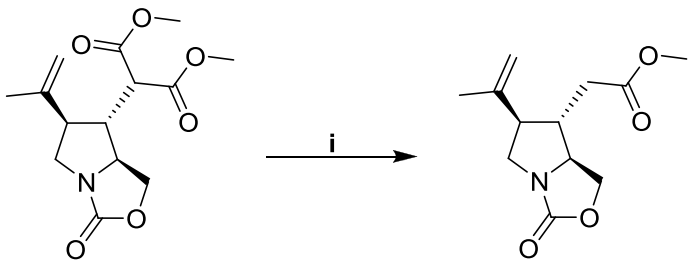
**Scheme 3.34**

### 3.3.3. A formal synthesis of allokainic acid 2.2.

The alkene **2.338** on decarboxylation would give rise to the formal synthesis of allokainic acid **2.2**. The molecule **2.338** was subjected to Krapcho decarboxylation (scheme 3.30). We performed the reaction (scheme 3.35) over a range of different temperatures, with similar conditions and results are summarised in **Table 3.2**.

In the **Table 3.2**, the reaction under different temperatures can be seen. The optimum temperature for this reaction is shown to be between 170 $^{o}$C - 175 $^{o}$C. If the temperature is above 175 $^{o}$C then the reactant is completely decomposed without any desired

product **2.233**. If the temperature is maintained below 170 $^{o}$C, then the reaction doesn't go to completion and we can recover the starting material **2.338**.




**2.338** **2.233**

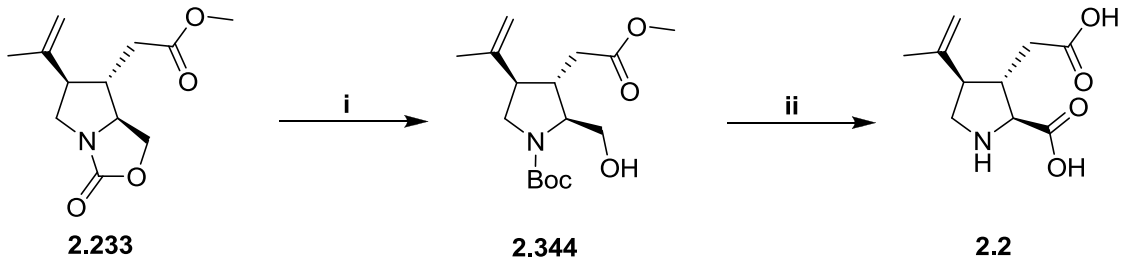
*Reagents and conditions*: i: NaCl, DMSO/$H_2O$, 170 $^{o}$C, 83%;

**Scheme 3.35**

**Table 3.2**. Krapcho reaction conditions

| **Rxn** | **Reagents and conditions** | **Temperature ($^{o}$C)** | **Time (h)** | **Inference** |
|---|---|---|---|---|
| 1) | **2.338** ,NaCl, DMSO/$H_2O$ | 140 | 8 | **2.338** |
| 2) | **2.338** ,NaCl, DMSO/$H_2O$ | 160 | 8 | Trace **2.233**, + **2.338**. |
| 3) | **2.338** ,NaCl, DMSO/$H_2O$ | 170 -175 | 8 | **2.233** (75 %) |
| 4) | **2.338** ,NaCl, DMSO/$H_2O$ | 180 -190 | 2 | Decomposed. |

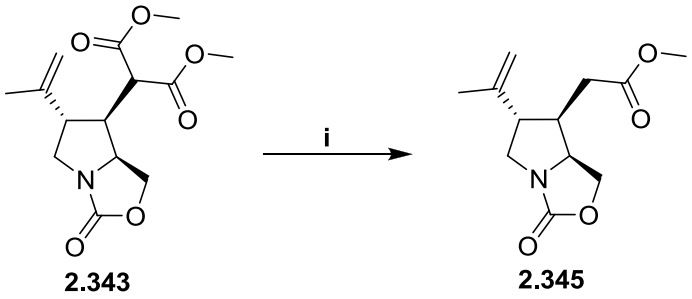
With the formation of **2.233**, we completed the formal synthesis of allokainic acid.[48,88] The opening of the oxazolidinone followed by oxidative deprotection gives allokainic acid **2.2** (scheme 3.36).




*Reagents and conditions*: i. NaOH, $(Boc)_2O$, $CH_2N_2$, 88%, overall; ii. Jones oxidation, $CH_2N_2$, 86%; iii. KOH, TFA, DOWEX $H^+$, 65%;

**Scheme 3.36**

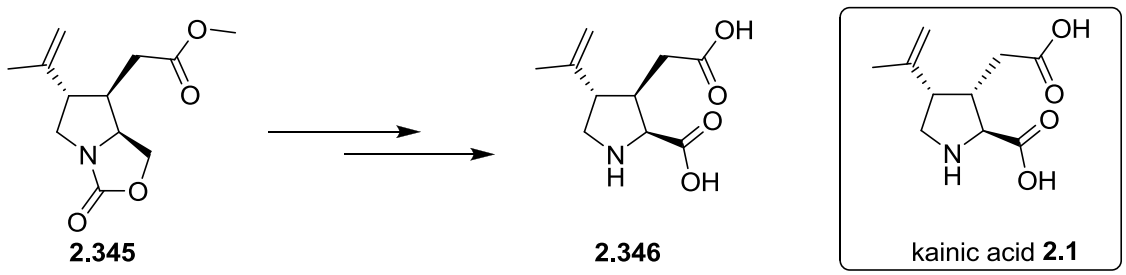
We performed the same decarboxylation with the opposite diastereomer **2.343** which gave the ester **2.345** (**s**cheme 3.37).




*Reagents and conditions*: i. NaCl, $DMSO/H_2O$, 170 $^oC$, 75%;

**Scheme 3.37**

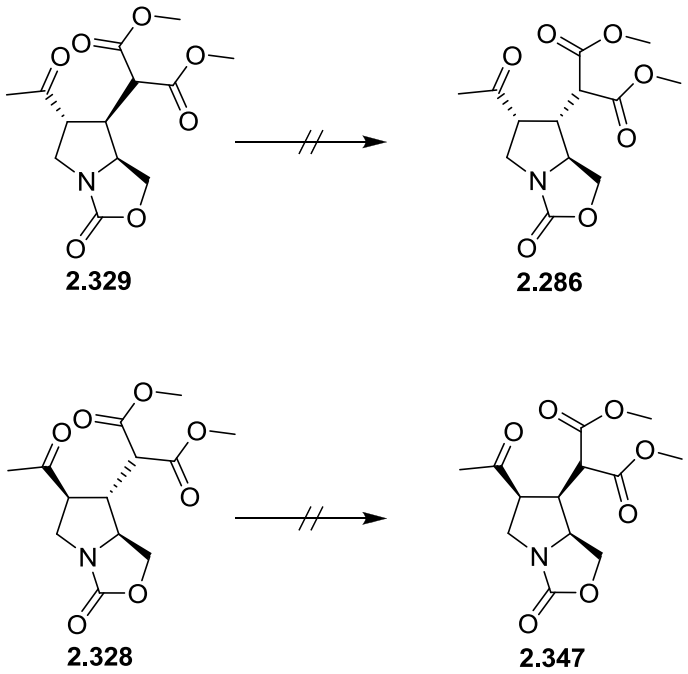
This ester **2.345** on further ring opening followed by oxidative deprotection would give the compound **2.346** which is the epimer of kainic acid **2.1** (scheme 3.38).




**Scheme 3.38**

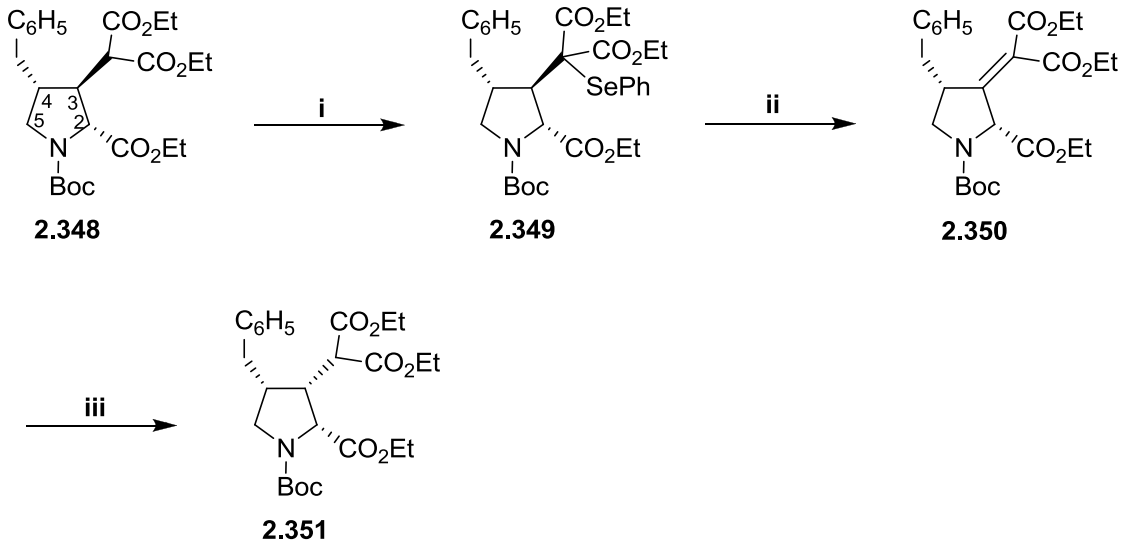
### 3.3.4. Attempts to change the stereochemistry at C-3 position.

Previous attempts were unsuccessful to change the stereochemistry at C-4 position (scheme 3.27). In our repeated attempts to convert the diastereomers **2.328** and **2.329** into cis-compounds **2.286** and **2.347** respectively, we found a suitable method developed by Almudena Rubio[59] which can be used to get the desired stereochemistry (scheme 3.39).




**Scheme 3.39**

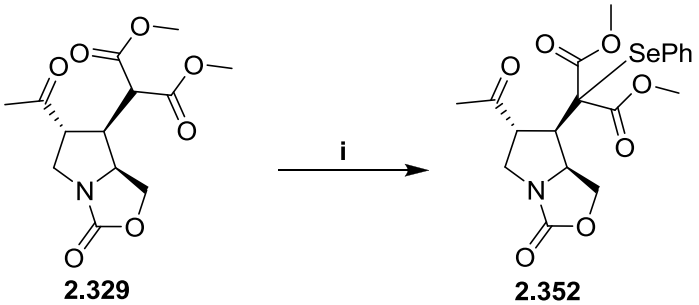
Almudena Rubio *et al.* using PhSeCl could adjust the stereochemistry at both the C-2 and C-3 positions of compound **2.348**. It started with the deprotonation of **2.348** with KHMDS in dry THF at 0 $^{o}$C which was then reacted with PhSeCl. The selenated product **2.349** was oxidized with hydrogen peroxide[128] in THF at 0 $^{o}$C, to give the olefin **2.350**. Asymmetric hydrogenation of the double bond was achieved in ethanol with $PtO_2$ as catalyst to give all-*cis* prolinate **2.351**. It should be noted that this final step required 15 days to reach completion (scheme 3.40).




*Reagents and conditions*: i. a) KHMDS/THF/0 $^{o}$C. b) PhSeCl/0 $^{o}$C – rt; ii. $H_2O_2$/THF/0 $^{o}$C; iii. $H_2$/$PtO_2$/EtOH;

**Scheme 3.40**

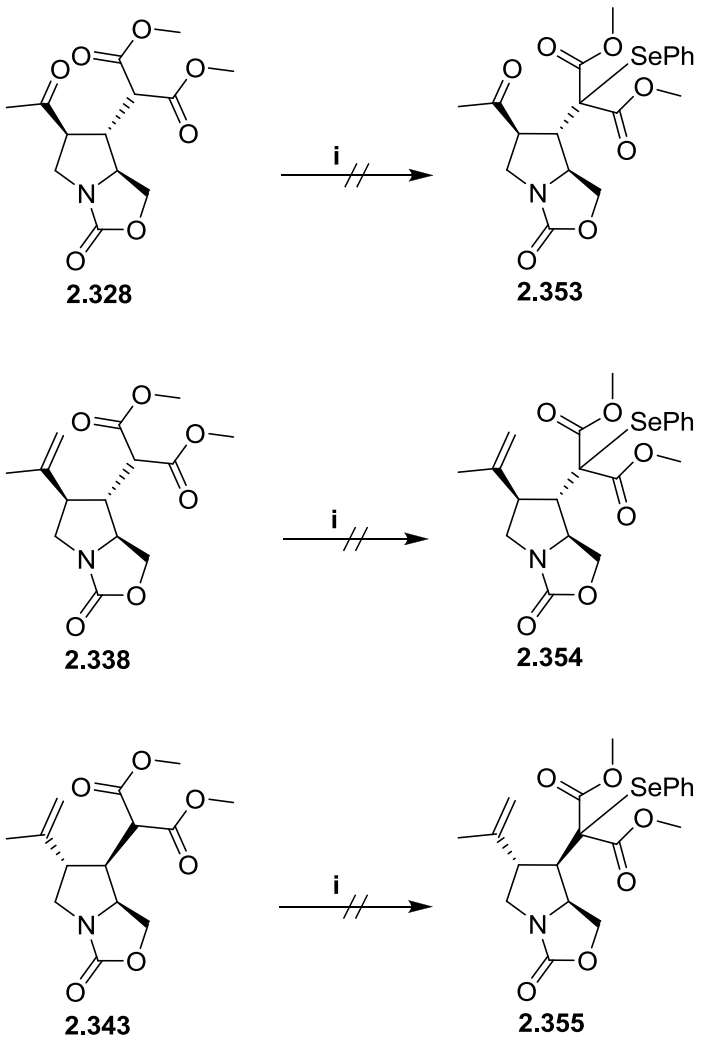
The change in stereochemistry to get the desired *cis* compounds **2.286** and **2.347** was prerequisite to complete the total synthesis of kainic acid **2.1**. Based on the work conducted by Rubio,[59] PhSeCl was reacted with **2.329** in the presence of KHMDS in THF at 0 $^{o}$C (scheme 3.41) to give selenated product **2.352**.




*Reagents and conditions*: i. KHMDS/THF/0 $^{o}$C, PhSeCl/0 $^{o}$C – rt, 78%;

**Scheme 3.41**

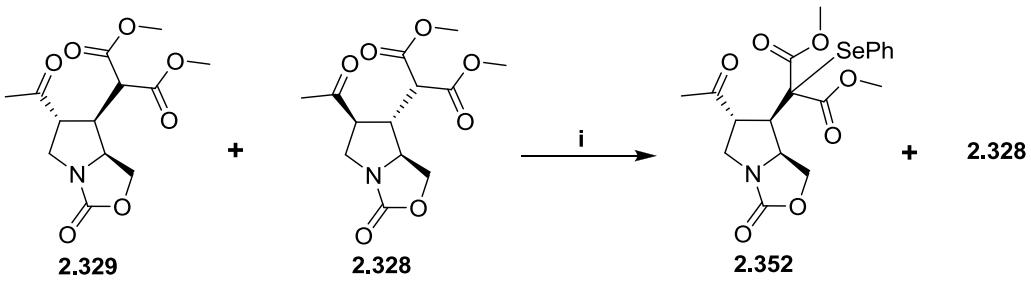
We tried an array of reactions using three separate oxazolidinone starting materials, all of which could further be useful in the synthesis of kainic acid **2.1**. However we failed to get any of the desired compounds and recovered the starting material (scheme 3.42).




*Reagents and conditions*: i. KHMDS/THF/0 $^{o}$C, PhSeCl/0 $^{o}$C – rt, starting material was recovered.

**Scheme 3.42**

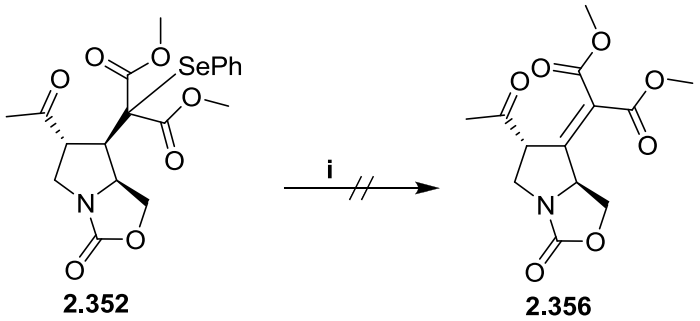
The same reaction conditions based on (scheme 3.41) were used on the mixture of the two diastereomers **2.329** and **2.328** and we got only one product **2.352** and the other diastereomer **2.328** remain unreacted (scheme 3.43).




*Reagents and conditions*: i. KHMDS/THF/0 $^{o}$C, PhSeCl/0 $^{o}$C – rt;

**Scheme 3.43**

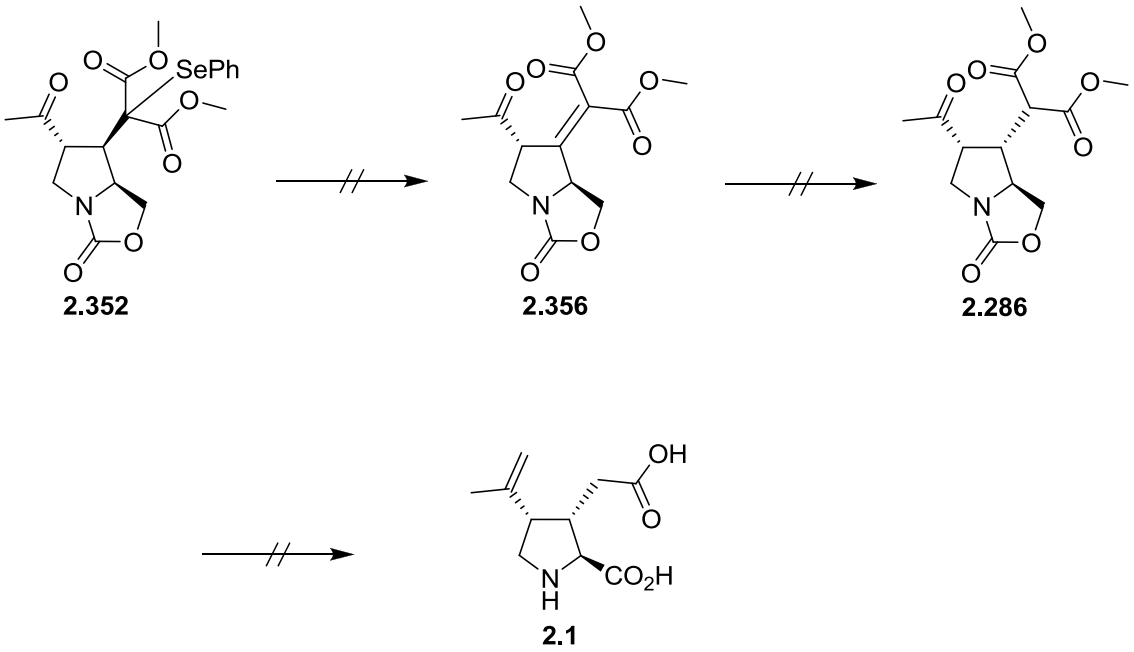
After the successful preparation of the selenated product **2.352**, the aim was to remove the PhSe group and form the double bond. We tried using $H_2O_2$/THF (scheme 3.44), but to no avail, the starting material decomposed and there were unidentifiable products formed.




*Reagents and conditions*: i. $H_2O_2$/THF/0 $^oC$;

**Scheme 3.44**

If successful in formation of **2.356,** it was more likely to give the required stereochemistry for the formation of kainic acid **2.1** (scheme 3.45).




**Scheme 3.45**

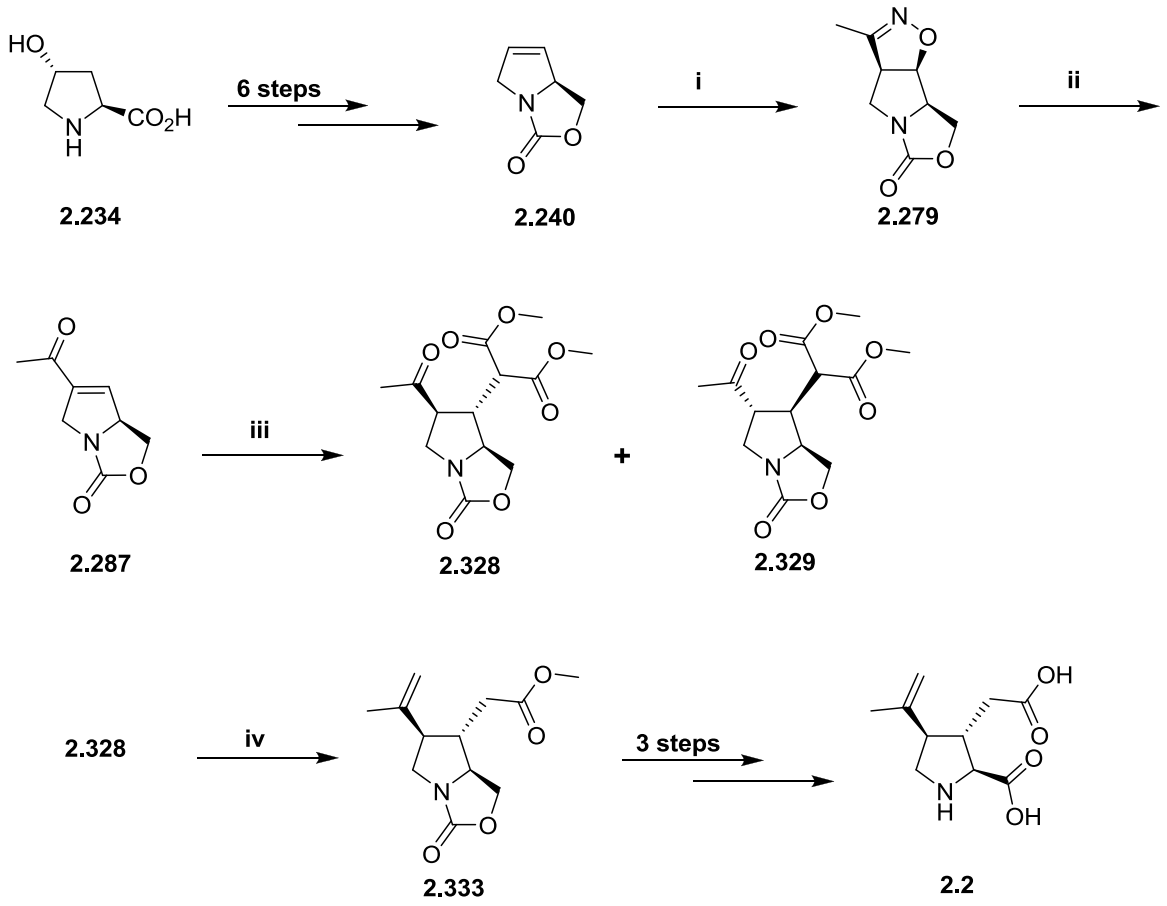
# 3.4. Conclusion:

An improved synthesis of oxazolidinone precursor **2.240** has been achieved. Some of the steps were improved by using alternative reagents or procedure and the overall yield of oxazolidinone **2.240** has been increased. Continuous studies on the stereoselective nature of oxazolidinone, gave us a novel unconventional product **2.290**.

The procedure in the formation of isoxazole **2.279** was improved compared to previous procedures. The formation of enone **2.287**, a key intermediate in the Michael addition reaction was successfully achieved in higher yield. The diastereomers **2.328** and **2.329** were successfully synthesised from enone **2.287** by Michael reaction, which could form the key intermediates for kainoids.

An attempt to change the stereocenters of C-3 and C-4 positions of diastereomers **2.328** and **2.329**, using different procedures was not successful. Although we were successful in the synthesis of selenated product **2.352**, we failed to remove the PhSe moiety to form the double bond.

We developed a novel route to the total synthesis of allokainic acid **2.2**. A formal synthesis of allokainic acid involving 11 steps with an overall yield of 9% has been reported (scheme 3.46). We have recently published much of this work used to synthesise allokainic acid **2.2**.[93]




*Reagents and conditions*: i. $EtNO_2$, TsCl, $Et_3N$, benzene, 12h, 68%; ii. (a) Raney Ni, $H_2$, Boric Acid, Methanol/Water (5:1), rt; (b) *p*-TSA·$H_2O$ , Toluene , reflux (80$^oC$), 89% overall yield; iii. NaH, THF, dimethyl malonate, 0 $^oC$ - rt, 90%, (**2.328**:**2.329** = 1:1); iv. (a) *n*-BuLi (2.5M), -78 $^oC$, $Ph_3PMeBr$/THF, (**2.338** =72%), (**2.329** = 10%). (b) NaCl, DMSO/$H_2O$, 170 $^oC$, 83%;

**Scheme 3.46**

# 4. Experimental

## 4.1. General Experimental Procedures

All experiments were performed under atmosphere of nitrogen unless otherwise stated, using oven dried glassware (or flame dried when necessary). Chemical reagents were commercially available and used without further purification unless otherwise stated.

Anhydrous diethyl ether and tetrahydrofuran were distilled from sodium in the presence of benzophenone. Dichloromethane, benzene, toluene, *N*,*N*-dimethylformamide, triethylamine, and ethyl acetate were distilled from calcium hydride prior to use. Methanol and ethanol were distilled from activated magnesium turnings using a crystal of iodine. Phenyl isocyanate was distilled from $P_2O_5$ and stored over flame-dried 3Å molecular sieves. All other grade solvents were used as received for routine purposes from Fischer scientific. Chemical reagents were commercially available, and used without further purification unless otherwise stated.

All reactions were monitored, where appropriate, by analytical Thin Layer Chromatography using Merck glass backed plates pre-coated with 0.25 mm layer of 60 $F_{254}$ silica gel. Visualisation was achieved with an Ultra Violet lamp (254 nm), and/or by staining with alkaline potassium permanganate, vanillin, or phosphomolybdic acid dips. Purification by flash column chromatography was carried according to Still procedure,[129] using Fisher Scientific silica 60A (35-70 mesh) with a pH of 6.5-7.5, eluting with solvent commercially available from Fischer scientific.

Proton nuclear magnetic resonance spectra ($^1$H NMR) were recorded using a Varian NMR System operating at 500 MHz. Samples were run at ambient probe temperature using $CDCl_3$ as the solvent, unless otherwise stated. Residual isotopic solvent ($CHCl_3$, $\delta_H$ = 7.27 ppm) was used as the internal reference. Chemical shifts (δ) are measured in parts per million (ppm), and coupling constants (*J*) are measured in Hertz (Hz). The following abbreviations are used to represent multiplicity of a given signal: s, singlet; d, doublet; t, triplet; m, multiplet; dd, doublet of doublets; ddd, double doublet of doublets; dt, doublet of triplets; br, broad singlet.

Carbon nuclear magnetic resonance spectra ($^{13}$C NMR) were recorded using a Varian NMR System operating at 125 MHz. Samples were run at ambient probe temperature

using $CDCl_3$ as the solvent, unless otherwise stated. Residual isotopic solvent ($CHCl_3$, $\delta_C$ = 77.00 ppm) was used as the internal reference. Chemical shifts (δ) are quoted in parts per million (ppm). Carbon spectra assignments are supported by DEPT, HSQC and correlation experiments.

The numbering of all the compounds mentioned in this section is arbitrary, with the sole intention to aid in the assignment of protons and carbons in the relevant spectra. They do not necessarily correspond with that of the I.U.P.A.C. guidelines.

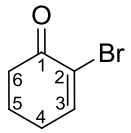
Infrared spectra (IR) were recorded on a Perkin-Elmer FT-IR 298 (1710) spectrometer, with absorption maxima ($\nu_{max}$) measured in $cm^{-1}$. Some samples were prepared as either a thin film (liquids) or a solution in dichloromethane (solids) between sodium chloride plates, and other samples were directly placed on a universal attenuated total reflectance sampling accessory.

Low and high resolution mass spectrometry data were recorded by Dr. Alaa Abdul-Sada on a Bruker Daltronics Apex III 4.7T using positive electro-spray ionization (+'ve ESI), and a Fisons Instrument VG Autospec using positive electron impact (+'ve EI), with methanol as the solvent. Only molecular ions, fractions from molecular ions and other major peaks are reported as mass/charge (m/z) ratios. The following abbreviations are used to describe the experiment: HRMS, high resolution mass spectrometry; LRMS, low resolution mass spectrometry. GC MS analyses were carried out on a Quattro micro GC using HP-5MS fused silica (30 m × 0.25 i. d. × 0.25 μm). The carried gas used was helium at a flow rate of 1 mL/min.

Optical rotations were recorded using a Bellingham-Stanley ADP440 polarimeter with a 1 cm-path length cell. Optical rotation $[\alpha]_D$ data are given in units $10^{-1}degcm^2g^{-1}$, and solution concentrations are given in $g/100\ cm^{-3}$.

## 4.2. Total synthesis of platensimycin 1.1

**2-bromocyclohex-2-enone 1.19.**




**1.19**

To a stirred solution of 10 mL (98.7 mmol) of 2-cyclohexenone **1.18** in 250 mL of DCM at 0 $^{o}$C was added dropwise 5.29 mL (103.2 mmol) of bromine in 100 mL of DCM over 30 min. The solution was stirred at 0 $^{o}$C for 1.5 hour, and then 23 mL (165 mmol) of $Et_3N$ was added dropwise. The solution was stirred at room temperature for 1.5 hour. The solution was washed with two 50 mL portions of 3% HCl and 50 mL of saturated brine. After the mixture was dried (using $MgSO_4$) and the solvent evaporated, there remained a crude solid. The crude solid was redissolved in DCM, treated with activated charcoal, and filtered, and the solvent was removed. Recrystallization from EtOAc and hexanes afforded 2-bromocyclohex-2-enone **1.19** as white crystals (12.2 g, 72%).

m.p.: 74-75 $^{o}$C.

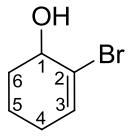
$^{1}$H NMR (500 MHz, $CDCl_3$): 7.41 (1H, t, $J$ = 6.2, H-3), 2.48-2.59 (2H, m, H-6), 2.37-3.41 (2H, m, H-4), 2.01-2.09 (2H, m, H-5).

$^{13}$C NMR (125.7 MHz, $CDCl_3$): 190.6 (C-1), 150.3 (C-3), 123.6 (C-2), 38.3 (C-6), 28.1 (C-4), 22.3 (C-5).

FTIR $\nu_{max}$ cm$^{-1}$ (neat): 1690 (C=O), 1600(C=C).

HRMS (ESI): *m/z* calculated for $C_6H_7{}^{79}BrO$ $[M]^+$ = 173.9680, found = 173.9682.

**2-bromocyclohex-2-enol 1.20.**




**1.20**

To a solution of 3.5 g of 2-bromo-cyclohex-2-enone **1.19** and 7 g of $CeCl_3 \cdot 7H_2O$ in 60 mL of MeOH, 0.78 g of solid $NaBH_4$ was added in small portions over half an hour. The mixture was stirred in room temperature for about 30 min. The compound was extracted using DCM and dried over anhydrous $MgSO_4$. The 2-bromocyclohex-2-enol **1.20** formed was colorless oil (2.7 g, 80%).

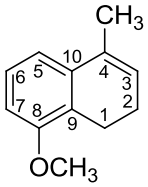
$^1$H NMR (500 MHz, $CDCl_3$): 6.21 (1H, t, *J* = 4.0, H-3), 4.22-4.18 (1H, m, H-1), 2.17 (1H, d, *J* = 4.1, OH), 2.08-1.99 (2H, m, H-4), 1.94-1.85 (2H, m, H-6), 1.74-1.64 (2H, m, H-5).

$^{13}$C NMR (125.7 MHz, $CDCl_3$): 132.3 (C-3), 125.7 (C-2), 69.9 (C-1), 32.1 (C-6), 27.8 (C-4), 17.7 (C-5).

FTIR $\nu_{max}$ cm$^{-1}$ (neat): 3361 (OH), 2938, 2866, 2830, 1640 (C=C), 1434, 1331, 1160

HRMS (ESI): *m/z* calculated for $C_6H_9BrO$ $[M]^+$ = 175.9837, found = 175.9847.

**8-methoxy-4-methyl-1,2-dihydronaphthalene 1.31**




**1.31**

To a solution of $CH_3MgBr$ in diethyl ether, 1 g (5.7 mmol) of 5-methoxy-1-tetralone **1.30** was added in small portions. The mixture was stirred and refluxed for 1 hour. The excess of the Grignard reagent was destroyed by slowly adding the mixture to a stirred saturated solution of ammonium chloride in water (50 mL). The organic phase was separated, dried and evaporated. The crude product obtained was treated with *p*-TSA (45.7 mmol) in toluene. After 30 min two layers were formed. The product was poured into 100 mL of water and 50 mL of ether. The organic phase was dried, the solvent was evaporated and distilled to obtain 8-methoxy-4-methyl-1,2-dihydronaphthalene **1.31** as colorless oil (800 mg, 79%).

$^1$H NMR (500 MHz, $CDCl_3$): 7.46-7.39 (1H, m, H-6), 6.94-6.88 (1H, m, H-5), 6.85-6.79 (1H, m, H-7), 5.89-5.82 (1H, m, H-3), 3.83 (3H, s, $OCH_3$), 2.84-2.78 (2H, m, H-1), 2.26-2.22 (2H, m, H-2), 2.15 (3H, s, $CH_3$).

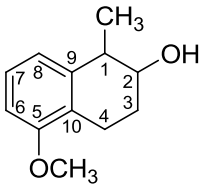
$^{13}$C NMR (125.7 MHz, $CDCl_3$): 158.1 (C-8), 138.6 (C-10), 135.4 (C-4), 132.5 (C-9), 128.3 (C-6), 116.3 (C-5), 114.1 (C-3), 112.4 (C-7), 56.3 ($OCH_3$), 26.1 (C-1), 25.2 (C-2), 19.7 ($CH_3$).

FTIR $\nu_{max}$ cm$^{-1}$(neat): 3054 (C-H), 2926 (C-H), 1573 (C=C), 1460, 1259.

HRMS (ESI): *m/z* calculated for $C_{12}H_{14}O$ $[M]^+$ = 174.1098, found = 174.1087.

.

**5-methoxy-1-methyl-1,2,3,4-tetrahydronaphthalen-2-ol 1.32**.




**1.32**

200 mg (1.04 mmol) of 8-methoxy-4-methyl-1,2-dihydronaphthalene **1.31** was added to 20 mL of diethyl ether and to the reaction mixture 1.4 mmol of $BH_3$·THF was added. The reaction mixture was stirred at 0 $^o$C for 1 h and then at rt for 16 hours. The reaction mixture was cooled to 0 $^o$C. To the reaction mixture 1 mL of $H_2O$ was added and 2 mL

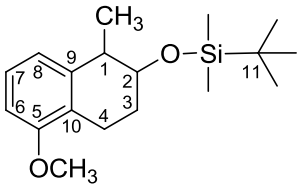
of 10% NaOH was added in one portion. Then 2 mL of 35% $H_2O_2$ solution was added. The reaction mixture was allowed to stir for 20 hours. The crude product was purified by column chromatography using 25% ether-petrol as solvent phase. After removal of the solvent 5-methoxy-1-methyl-1,2,3,4-tetrahydronaphthalen-2-ol **1.32** was crystallized using ethyl acetate and methanol (160 mg, 71%). The X-Ray crystallographic studies confirmed the structure (figure 1.3).

$^1$H NMR (500 MHz, $CDCl_3$): 6.81-6.75 (1H, m, H-7), 6.54-6.49 (1H, m, H-8), 6.47-6.44 (1H, m, H-6), 3.85 (3H, s, $OCH_3$), 3.55 (1H, s, OH), 3.35-3.31 (1H, m, H-2), 3.13-3.09 (1H, m, H-1), 2.87-2.83 (2H, m, H-4), 1.84-1.79 (2H, m, H-3), 1.22 (2H, s, $CH_3$).

$^{13}$C NMR (125.7 MHz, $CDCl_3$): 157.2 (C-5), 136.7 (C-9), 126.8 (C-7), 126.1 (C-10), 117.8 (C-8), 108.9 (C-6), 70.9 (C-2), 56.2 ($OCH_3$), 40.2 (C-1), 28.4 (C-3), 18.9 (C-4), 16.9 ($CH_3$).

HRMS (ESI): *m/z* calculated for $C_{12}H_{16}O_2Na$ $[M^+Na]^+$ = 215.1058, found = 215.1074.

### *tert*-butyl(5-methoxy-1-methyl-1,2,3,4-tetrahydronaphthalen-2-yloxy)dimethylsilane 1.27




**1.27**

To a stirred solution of 5-methoxy-1-methyl-1,2,3,4-tetrahydronaphthalen-2-ol **1.32** (100 mg, 0.33 mmol) in dry DCM (10 mL) at 0 ºC was added *tert*-butyldimethylsilyl chloride (58 mg, 0.39 mmol) and imidazole (56 mg, 0.82 mmol). After 1 hour, the reaction mixture was quenched with water. The phases were separated and the aqueous phase was extracted twice with DCM. The organic layers were combined, washed once with water, washed once with brine, dried over anhydrous sodium sulphate and

concentrated under reduced pressure to give a colourless liquid. Distillation under reduced pressure afforded *tert*-butyl(5-methoxy-1-methyl-1,2,3,4-tetrahydronaphthalen-2-yloxy)dimethylsilane **1.27** as brown oil (127 mg 80%).

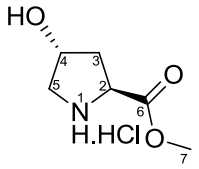
$^{1}$H NMR (500 MHz, $CDCl_3$): 6.83-6.78 (1H, t, H-7), 6.51-6.48 (1H, m, H-8), 6.46-6.42 (1H, m, H-6), 3.83 (3H, s, $OCH_3$), 3.33-3.29 (1H, m, H-2), 3.11-3.08 (1H, m, H-1), 2.89-2.82 (2H, m, H-4), 1.86-1.83 (2H, m, H-3), 1.24 (2H, s, $CH_3$), 0.97 (9H, s, $SiC(CH_3)_3$), 0.20 (6H, s, $Si(CH_3)_2$).

$^{13}$C NMR (125.7 MHz, $CDCl_3$): 157.4 (C-5), 136.9 (C-9), 126.8 (C-7), 126.1 (C-10), 117.9 (C-8), 109.1 (C-6), 83.5 (C-2), 56.1 ($OCH_3$), 41.5 (C-1), 30.8 (C-11), 29.5 (C-3), 26.0 ($SiC(\underline{C}H_3)_3$), 19.1 (C-4), 16.6 ($CH_3$).

Ion not found.

## 4.3. Synthesis of oxazolidinone 2.240

**(2*S*,4*R*)-methyl 4-hydroxypyrrolidine-2-carboxylate hydrochloride 2.235**




The title compound was prepared by a modification of the procedure of Jason Lai.[96]

To a stirred suspension of *trans*-4-hydroxy-L-proline **2.234** (10.0 g, 76.0 mmol) in methanol (40 mL), thionyl chloride (2.49 mL, 34.31 mmol) was added drop wise at 0 $^{o}$C. The reaction mixture was stirred at 0 $^{o}$C for 1 hour before being heated at reflux for 24 hours, and re-cooled to 0 $^{o}$C. The mixture was diluted with diethyl ether (80 mL). The white precipitate obtained was filtered, washed with diethyl ether (2 x 20 mL) and dried under reduced pressure to give methyl (4*R*)-4-hydroxy-L-prolinate hydrochloride **2.235** as a white solid (11.5 g, 83%).

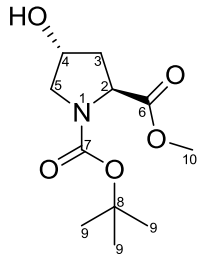
$^{1}$H NMR (500 MHz, DMSO) δ (Doubling and broad peaks as a result of rotamers): 4.46 (1H, dd, *J* = 10.6 and 7.6, H-2), 4.38 (1H, m, H-4), 3.74 (3H, m, H-7), 3.33-3.06 (2H, (3.06 (d, *J* =12.1, 1H)), H-5), 2.17-2.06 (2H, m, 3-H).

$^{13}$C NMR (126 MHz, DMSO) δ (Doubling and broad peaks as a result of rotamers): 169.4 (C-6), 68.9 (C-4), 58 (C-2), 53.6 (C-7), 53.4 (C-5), 37.5 (C-3).

FTIR $\upsilon_{max}$ $cm^{-1}$(neat): 3321 (sharp, OH-free), 1739 (C=O of ester).

HRMS (ESI): *m/z* calculated for $C_6H_{12}NO_3$ $[M]^+$ = 146.0812, found = 146.0811.

**(2*S*,4*R*)-1-*tert*-butyl 2-methyl 4-hydroxypyrrolidine-1,2-dicarboxylate 2.236**




The title compound was prepared by a modification of the procedure of Jason Lai.[96]

Diisopropylethylamine (57.5 mL, 330.34 mmol) and di-*tert*-butyl dicarbonate (63.0 g, 289.24 mmol) were added to a suspension of (2*S*,4*R*)-methyl 4-hydroxypyrrolidine-2-carboxylate hydrochloride **2.235** (50 g, 342.2 mmol) in DCM (500 mL) at 0 $^{o}$C. The reaction mixture was allowed to warm to room temperature and stirred for 24 hours before being concentrated under reduced pressure. The residue formed was diluted with ethyl acetate (250 mL), and saturated ammonium chloride solution (250 mL) was added. The aqueous phase was further extracted with ethyl acetate (3 x 300 mL). The organic phases were combined, and washed with saturated sodium hydrogen carbonate (1000 mL), brine (1000 mL), and dried over magnesium sulfate. The resultant solution was concentrated under reduced pressure to give (2*S*,4*R*)-1-*tert*-butyl 2-methyl 4-hydroxypyrrolidine-1,2-dicarboxylate **2.236** as a yellow oil (58.3 g, 86.3%). This was used without any further purification.

$^{1}$H NMR (500MHz, $CDCl_3$) δ (Doubling and broad peaks as a result of rotamers): 4.48 (1H, m, H-4), 4.39 (1H, t, *J* = 7.9, H-2), 3.72(3H, s, H-10), 3.63-3.44 (2H, m, H-5), 2.28 (1H, m, H-4), 2.08 (2H, m, H-3), 1.43 (9H, 2s, H-9).

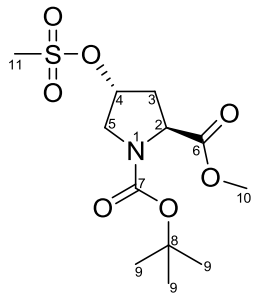
$^{13}$C NMR (126 MHz, $CDCl_3$) δ (Doubling and broad peaks as a result of rotamers): 173.6 (C-6), 154.0 (C-7), 80.4 and 80.3 (C-8), 70 and 69.3 (C-4), 57.9 and 57.4 (C-2), 54.6 (C-5), 52.8 (C-10), 39.1 and 38.4 (C-3), 28.3 and 28.2 (C-9).

FTIR $\upsilon_{max}$ $cm^{-1}$(neat): 3322 (O-H sharp, OH free), 1740 (C=O).

HRMS (ESI+): *m/z* calculated for $C_{11}H_{19}NO_5Na$ $[M+Na]^+$ = 268.1155 found = 268.1154.

Spectroscopic data identical to literature values.[95,96]

**(2*S*,4*R*)-1-*tert*-butyl 2-methyl 4-(methylsulfonyloxy)pyrrolidine-1,2-dicarboxylate 2.241.**




The title compound was prepared by a modification of the procedure of Jason Lai.[96]

Methanesulfonyl chloride (21.5 g, 188.2 mmol) and 4-dimethylaminopyridine (2.1 g, 17.1 mmol) were added to a stirred solution of 1-*tert*-butyl 2-methyl (2*S* ,4*R*)-4-hydroxypyrrolidine-1,2-dicarboxylate **2.236** (41.9 g, 171.11 mmol) and triethylamine (25.7 mL, 184.8 mmol) in DCM (600 mL) at 0 $^{o}$C. The reaction mixture was stirred and allowed to warm to room temperature for 15 hours before cooling to 0 $^{o}$C and adding water (300 mL). The phases were separated and the aqueous phase was extracted with DCM (3 x 200 mL). The organic extracts were combined and washed with 1M citric

acid solution, saturated sodium hydrogen carbonate solution and dried over magnesium sulfate. The extract was concentrated under reduced pressure. The crude product obtained was purified by flash column chromatography on silica gel, eluting with 50% ethylacetate / petrol gave 1-*tert*-butyl 2-methyl(2*S*,4*R*)-4-[(methylsulfonyl)oxy]pyrrolidine-1,2-dicarboxylate **2.241** as a white solid (45.4 g, 82%). This was used without any further purification.

$^{1}$H NMR (500 MHz, CDCl3) δ (Doubling and broad peaks as a result of rotamers): 5.28 (1H, m, H-4), 4.45 (1H, dt, *J* = 33.9 and 7.9, H-2), 3.86-3.78 (2H, m, H-5), 3.76 (3H, s, H-10), 3.06 (3H, s, H-11), 2.66-2.57 (1H, m, H-3), 2.27 (1H, m, H-3), 1.47-1.44 (9H, 2 x s, H-9).

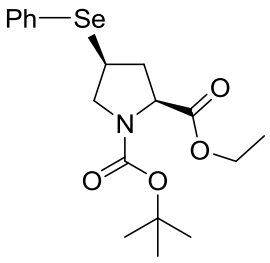
$^{13}$C NMR (126 MHz, CDCl3) δ (Doubling and broad peaks as a result of rotamers): 172.9 (C-6), 153.5 (C-7), 80.8 (C-8), 77.9 (C-4), 57.5 (C-2), 52.5 (C-10), 52.3 (C-5), 38.8 (C-11), 37.5 (C-3), 28.4 (C-9).

FTIR $\upsilon_{max}$ cm$^{-1}$(neat): 2972 (O-$SO_2CH_3$ , 1745 (C=O), 1696 (C=O).

HRMS (ESI+): *m/z* calculated for $C_{12}H_{21}NO_7SNa$ $[M+Na]^+$ = 346.0931 found = 346.0928.

Spectroscopic data identical to literature values.[95,96]

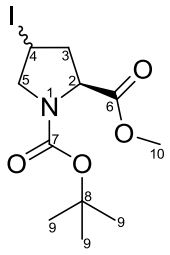
**(2*S*,4*S*)-1-*tert*-butyl 2-ethyl 4-(phenylselanyl)pyrrolidine-1,2-dicarboxylate 2.242**




The title compound was prepared by a modification of the procedure of Jason Lai.[96]

Sodium borohydride (6.35 g, 167.8 mmol) was added to a stirred suspension of diphenyl diselenide (22.9 g, 76.9 mmol) in anhydrous ethanol (750 mL) at 0 $^{o}$C portion wise. The reaction mixture was allowed to warm to room temperature and stirred for one hour before re-cooling to 0 $^{o}$C. The solution of 1-*tert*-butyl 2-methyl (2*S*,4*R*)-4-[(methylsulfonyl)oxy]pyrrolidine-1,2-dicarboxylate **2.241** (45.2 g, 139.9mmol) in anhydrous ethanol (250 mL) was added to the reaction mixture followed by heating at reflux for 24 hours. The reaction mixture was concentrated under reduced pressure, re-diluted with diethyl ether (1000 mL) and washed with water (600 mL). The phases were separated and the aqueous phase was extracted with diethyl ether (3 x 500 mL). The organic phases were combined and further washed with saturated sodium chloride solution (600 mL), dried over magnesium sulphate and concentrated under reduced pressure to give the crude (2*S*,4*S*)-1-*tert*-butyl 2-ethyl 4-(phenylselanyl)pyrrolidine-1,2-dicarboxylate **2.242** as a brown oil (51.5 g, 92%). This compound was not isolated. This was used without any further purification.

**(2*S*)-1-*tert*-butyl 2-methyl 4-iodopyrrolidine-1,2-dicarboxylate 2.237.**




(2*S*,4*R*)-1-tert-butyl 2-methyl 4-hydroxypyrrolidine-1,2-dicarboxylate **2.236**, 500 mg (1.9 mmol) was dissolved using stirring and a little heat in toluene (5 mL) and acetonitrile (3 mL). The mixture was cooled to 0 $^{o}$C, and triphenyl phosphine (1.57 g, 6mmol), imidazole (0.82 g, 12.1 mmol) and iodine (1.58 g 6.2 mmol) were added. After 24 hours, the mixture was filtered and the filtrate was reduced under low pressure. Diethyl ether (5 mL) was added to precipitate remaining triphenylphophine oxide which was removed by filtration. Residual iodine was removed from the filtrate by washing with sodiumthiosulfate (5 mL). The organic layer was reduced at low pressure and the iodinated pyrrolidine **2.237** was purified by flash chromatography, starting with 100%

hexane and then 2:1 ethyl acetate and hexane to give (2*S*)-1-*tert*-butyl 2-methyl 4-iodopyrrolidine-1,2-dicarboxylate **2.237** as a mixture of white crystalline solid and yellow oil (620 mg, 88%).

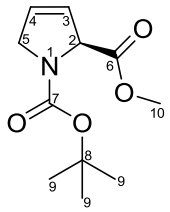
$^{1}$H NMR (500MHz, $CDCl_3$) δ (Doubling and broad peaks as a result of rotamers): 4.46-4.32 (1H, m, H-4), 4.06 (1H, m, H-2), 3.90-3.71 (2H, m, H-5), 3.74 (3H, s, H-10), 2.56-2.39 (2H, m, H-3), 1.43-1.40 (9H, 3xs, H-9).

$^{13}$C NMR (126 MHz, CDCl3) δ (Doubling and broad peaks as a result of rotamers): 172.8(C-6), 153.2(C-7), 80.6(C-8), 58.7 (C-4), 58.5(C-2), 57.4 (C-5), 52.3 (C-10), 42.6 (C-3), 28.4 (C-9).

FTIR $\upsilon_{max}$ $cm^{-1}$(neat): 1698.69 (C=O).

HRMS (ESI+): *m/z* calculated for $C_{11}H_{18}INO_4Na$ $[M+Na]^+$ = 378.0173 found = 378.0187.

**(*S*)-1-*tert*-butyl 2-methyl 1*H*-pyrrole-1,2(2*H*,5*H*)-dicarboxylate 2.238.**




DBU (0.22 g, 1.4 mmol) was added to a flask containing a stirring solution of toluene (5 mL) and (2*S*)-1-*tert*-butyl 2-methyl 4-iodopyrrolidine-1,2-dicarboxylate **2.237** (500mg, 1.3 mmol). The mixture was stirred and heated to 85 $^{o}$C for over 7 hours to give a white precipitate. The reaction mixture was filtered to remove the shining white powder and the filtrate was concentrated under reduced pressure to give a crude orange oil. The oil was purified by flash chromatography using 1:20 ethyl acetate and hexane and slowly increasing to 1:1 to give (*S*)-1-*tert*-butyl 2-methyl 1*H*-pyrrole-1,2(2*H*,5*H*)-dicarboxylate **2.238** as yellow oil (250 mg, 75%).

$^{1}$H NMR (500MHz, $CDCl_3$) δ (Doubling and broad peaks as a result of rotamers): 6.02-5.89 (1H, m, H-4), 5.78-5.71 (1H, m, H-3), 5.06-4.92 (1H, m, H-2), 4.32-4.14 (2H, m, H-5), 3.75 (3H, s, H-10), 1.48 and 1.43 (9H, 2 x s, H-9)

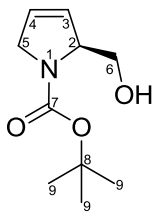
$^{13}$C NMR (126 MHz, $CDCl_3$) δ (Doubling and broad peaks as a result of rotamers): 171.0(C-6), 153.1(C-7), 129.3 and 129.2 (C-4), 124.7 and 124.6 (C-3), 80.1 and 80.09 (C-8), 66.5 and 66.1 (C-2), 53.4 and 53.2 (C-10), 52.5 and 52.07(C-5), 28.3 and 28.2 (C-9).

FTIR $\upsilon_{max}$ $cm^{-1}$(neat): 2986 (=C-H st), 1704 (C=O).

HRMS (ESI+): *m/z* calculated for $C_{11}H_{17}NO_4Na$ $[M+Na]^+$ = 250.1050 found = 250.1047.

Spectroscopic data identical to literature values.[95,96]

**(*S*)-*tert*-butyl 2-(hydroxymethyl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate 2.239.**




The title compound was prepared by a modification of the procedure of Jason Lai.[96]

(*S*)-1-*tert*-butyl 2-methyl 1*H*-pyrrole-1,2(2*H*,5*H*)-dicarboxylate **2.238** (2 g, 8 mmol), was dissolved in a mixture of THF (18 mL) and anhydrous methanol (9 mL). The solution was cooled to 0 $^{o}$C. Sodium Borohydride (1 g, 26.4 mmol) was added via a solid addition tube over an hour. The reaction was gradually warmed to room temperature and was allowed to stir overnight. The reaction mixture was again cooled to 0 $^{o}$C and a saturated ammonium chloride solution was added drop wise. The solvents were removed under reduced pressure. The remaining aqueous phase was filtered through Celite® and washed with ethyl acetate. The layers were separated and the aqueous phase was extracted with ethyl acetate and organic fractions were dried over

magnesium sulphate. The solvents were removed under reduced pressure to give (*S*)-*tert*-butyl 2-(hydroxymethyl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate **2.239** as an viscous orange oil (1.52 g, 85%).

$^{1}$H NMR (500 MHz, $CDCl_3$) δ (Doubling and broad peaks as a result of rotamers): 5.93-5.81(1H, m, H-4), 5.69-5.62(1H, m, H-3), 4.74-4.58(1H, m, H-2), 4.58(1H, s, OH), 4.18(1H, d, *J* = 15.7, H-5), 4.12-4.06(1H, m, H-5), 3.78(1H, t, *J* = 9.4, H-6), 3.60-3.54(1H, m, H-6), 1.50(9H, s, H-9).

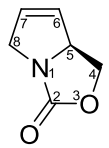
$^{13}$C NMR (126 MHz, $CDCl_3$) δ (Doubling and broad peaks as a result of rotamers): 156.5 (C-7), 126.7 (C-3), 126.67 ( C-4), 80.5 (C-8), 67.6 (C-2), 67.1 (C-5), 54.1 (C-6), 28.4 (C-9).

FTIR $\upsilon_{max}$ $cm^{-1}$(neat): 3432 (O-H broad, H-bonded), 2982 (=C-H st), 1673 (C=O).

HRMS (ESI+): *m/z* calculated for $C_{10}H_{17}NO_3Na$ $[M+Na]^+$ = 222.1101 found = 222.1095.

Spectroscopic data identical to literature values.[95,96]

**(*S*)-1,7*a*-dihydropyrrolo[1,2-*c*]oxazol-3(5*H*)-one 2.240.**




The title compound was prepared by a modification of the procedure of Jason Lai.[96]

To a flask containing (*S*)-*tert*-butyl 2-(hydroxymethyl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate **2.239** (5.69 g, 25.6 mmol) in anhydrous DCM (100 mL) flushed with $N_2$ gas and cooled to 0 $^{o}$C, DAST was added(4.59 mL in 25 mL DCM 28.5 mmol) dropwise over an hour. The mixture was allowed to warm to room temperature and stirred for nearly 16 hrs before cooling again to 0 $^{o}$C. To this reaction mixture aqueous sodium bicarbonate (70 mL) was added slowly. The layers were separated and the aqueous phase was extracted with DCM (3 x 100 mL). The combined organic fractions

were washed with ammonium chloride (100 mL) and dried with magnesium sulfate. The resultant organic fraction was concentrated under reduced pressure. This was purified by flash chromatography using 7:1 ether, hexane to give (S)-1,7*a*-dihydropyrrolo[1,2-*c*]oxazol-3(5*H*)-one **2.240** as a brown oil (3.1 g, 86%).

$^{1}$H NMR (500 MHz): 6.06-6.04 (1H, m, H-7), 5.91-5.90 (1H, m, H-6), 4.75-4.70 (1H, m, H-5), 4.60 (1H, t, *J* = 8.7, H-4), 4.42-4.38 (1H, m , H-8), 4.24 (1H, dd, *J* = 8.6, 5.1, H-4), 3.84-3.80 (1H, m, 8-H).

$^{13}$C NMR( 125.7 MHz, $CDCl_3$): 163.3 (C-2), 130.9 (C-7), 128.9 (C-6), 68.7 (C-4), 64.6 (C-5), 54.8 (C-8).

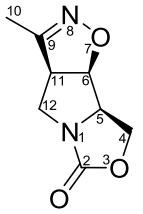
FTIR $\upsilon_{max}$ $cm^{-1}$ (neat): 2920 (=C-H st), 1738 (C=O).

HRMS (ESI+): *m/z* calculated for $C_6H_7NO_2Na$ $[M+Na]^+$ = 148.0369 found = 148.0816.

Spectroscopic data identical to literature values.[95,96]

## 4.4. Synthesis of enone 2.287.

### (*Z*)-6-(1-(methoxyimino)ethyl)tetrahydropyrrolo[1,2-*c*]oxazol-3(1*H*)-one 2.279.




The title compound was prepared by a modification of the procedure of Jason Lai.[96]

Triethylamine (162 mg, 1.6 mmol) was added to a stirred solution of (*S*)-1,7*a*-dihydropyrrolo[1,2-*c*]oxazol-3(5*H*)-one **2.240** (100 mg, 0.8 mmol), nitroethane (72 mg, 0.96 mmol) and *p*-toluene sulphonyl chloride (305 mg, 1.6 mmol) in benzene (20 mL) at 0 $^{o}$C. The reaction mixture was allowed to warm to room temperature and left to stir for 12 hours. The solvents were removed under reduced pressure and further purified

using flash chromatography using 1:1 hexane and ethyl acetate, followed by neat ethyl acetate to give (*Z*)-6-(1-(methoxyimino)ethyl)tetrahydropyrrolo[1,2-*c*]oxazol-3(1*H*)-one **2.279** as a white crystalline solid (98 mg, 68%). The X-Ray crystallographic studies confirmed the structure (figure 3.7).

TLC, Rf = 0.36. (100% EtOAc).

m.p.: 123.1-127.4 $^{o}$C.

$[\alpha]_D$ -1.66° (*c* 1.0, $CH_2Cl_2$).

$^1$H NMR (500 MHz) : 5.06 (1H, dd, *J* = 8.5, 4.8, H-6), 4.69 (1H, dd, *J* = 8.9, 2.6, H-4), 4.48 (1H, t, *J* = 8.6, H-4), 4.06 (1H, m, H-12), 4.05 (1H, m, H-5), 3.82 (1H, t, *J* = 8.1, H-11), 3.27 (1H, dd, *J* = 12.9, 7.6 Hz, H-12).

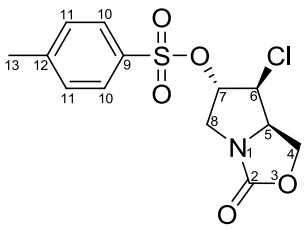
$^{13}$C NMR (125.7 MHz, $CDCl_3$): 176.9 (C-2), 155.1 (C-9), 83.6 (C-6), 64.3 (C-4), 62.6 (C-5), 58.1 (C-11), 48.0 (C-12), 11.3 (C-10).

FTIR $\upsilon_{max}$ cm$^{-1}$(neat): 2922 (=C-H st), 1737 (C=O), 1462 ($CH_2$), 1191 (C-O), 993 (N-O), 777.

HRMS (ESI+): *m/z* calculated for $C_8H_{10}N_2O_3Na$ $[M+Na]^+$ = 205.0583 found = 205.0584

Spectroscopic data identical to literature values.[96]

**(6*S*,7*S*)-7-chloro-3-oxohexahydropyrrolo[1,2-*c*]oxazol-6-yl 4-methylbenzenesulfonate 2.290**




During the preparation of **2.279**, the solvent benzene was replaced with DCM, and under the same reagents and conditions used for the preparation of **2.279**, the byproduct

(6*S*,7*S*)-7-chloro-3-oxohexahydropyrrolo[1,2-*c*]oxazol-6-yl 4-methylbenzenesulfonate **2.290** was isolated as a crystalline solid (1 g, 15%). The X-Ray crystallographic studies confirmed the structure (figure 3.5).

TLC, (EtOAc) Rf = 0.35.

m.p.: 148.1-149.5 $^{o}$C.

$[\alpha]_D$ +3.78° (*c* 1.0, $CHCl_3$).

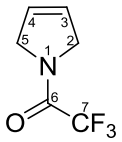
$^1$H NMR (500 MHz, $CDCl_3$) δ: 7.81 (2H, d, *J* = 8.3, H-10), 7.41 (2H, d, *J* = 8.4, H-11), 5.12 (1H, d, *J* = 5.3, H-7), 4.59-4.55 (1H, m, H-4), 4.48 (1H, dd, *J* = 9.5, 2.7, H-4), 4.45 (1H, dt, *J*= 8.3, 2.9, H-6), 4.38 (1H, d, *J*= 3.1, H-5) 4.02 (1H, dd, *J* = 13.5, 5.3, H-13), 3.2 (1H, d, *J* = 13.5, H-8).

$^{13}$C NMR( 125.7 MHz, $CDCl_3$) δ: 160.7 (C-2), 146.1 (C-8), 132.5 (C-12), 130.4 (2C, C-10), 127.9 (2C, C-11), 84.8 (C-7), 63.6 (C-4), 61.6 (C-6), 61.3 (C-5), 50.40 (C-8), 21.7 (C-13).

FTIR $\upsilon_{max}$ cm$^{-1}$(neat): 2978 (O-$SO_2$-Ph) , 1749 (C=O).

HRMS (ESI+): *m/z* calculated for $C_{13}H_{14}ClNO_5SNa$ $[M+Na]^+$ = 354.0173 found = 354.0174.

**1-(2,5-dihydro-1*H*-pyrrol-1-yl)-2,2,2-trifluoroethanone 2.302.**




The title compound was prepared by the modification procedure described by Carl B Ziegler.[130]

3-pyrroline (10 g, 144.9 mmol) was dissolved in a mixture of pyridine (15 mL) and diethyl ether (30 mL) and to the reaction mixture trifluoroacetic anhydride (22 mL) was added dropwise over a period of 1 hour. The reaction mixture was stirred at room temperature for an additional hour and the pyridiniumtrifluoroacetate salt obtained was

removed by filteration. The filtrate was evaporated to an oily residue which was distilled (36$^{o}$C /3.5- mmHg) to give 1-(2,5-dihydro-1*H*-pyrrol-1-yl)-2,2,2-trifluoroethanone **2.302** as deep blue coloured oil (14 g, 61%).

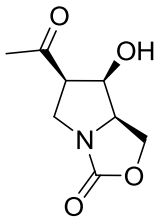
$^{1}$H NMR (500 MHz, $CDCl_3$) δ: 5.90 - 5.83 (2H, m, H-3 and H-4), 4.47 - 4.36 (4H, m, H-2 and H-5).

$^{13}$C NMR( 125.7 MHz, $CDCl_3$) δ: 155.3 (C-6), 124.8 and 124.6 (C-3 and C-4), 117.4 and 115.1 (C-7), 54.6 and 53.0 (C-2 and C-5).

FTIR $\upsilon_{max}$ cm$^{-1}$(neat): 1688 (C=O), 1462 ($CH_2$), 1133 (C-C).

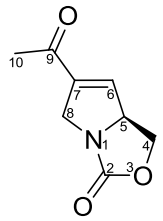
HRMS (ESI+): *m/z* calculated for $C_6H_6NONa$ $[M+Na]^+$ = 188.0294 found =188.0292.

**(6*R*,7*R*)-6-acetyl-7-hydroxytetrahydropyrrolo[1,2-*c*]oxazol-3(1*H*)-one 2.288.**




Raney®-nickel (10-20 mg) was added to the (Z)-6-(1-(methoxyimino)ethyl)tetrahydropyrrolo[1,2-*c*]oxazol-3(1*H*)-one **2.279** (680 mg, 3.7 mmol) and boric acid (485 mg, 7.8 mmol), in 5:1 mixture of methanol and water (30 mL). The reaction mixture was allowed to stir for 8 h under hydrogen atmosphere. The Raney®-nickel was removed by filtration using Celite®. The solvent was removed under reduced pressure and the product (6*R*,7*R*)-6-acetyl-7-hydroxytetrahydropyrrolo[1,2-c]oxazol-3(1H)-one **2.288** was used in next step without further purification. This compound was not isolated.

**(*S*)-6-acetyl-1,7a-dihydropyrrolo[1,2-*c*]oxazol-3(5*H*)-one 2.287.**




To a flask containing (6*R*,7*R*)-6-acetyl-7-hydroxytetrahydropyrrolo[1,2-*c*]oxazol-3(1*H*)-one **2.288** in toluene, a catalytic amount of *p*-TSA·$H_2O$ (3 mg) was added and refluxed using Dean-Stark apparatus for 8 h. After 8 h, the product in toluene was extracted using DCM and concentrated under reduced pressure. The resultant crude was further purified using flash chromatography with 9:1 ethyl acetate and hexane to give (*S*)-6-acetyl-1,7a-dihydropyrrolo[1,2-*c*]oxazol-3(5*H*)-one **2.287** as brown solid (560 mg, 89%). The X-Ray crystallographic studies confirmed the structure (figure 3.4).

TLC, (EtOAc) Rf = 0.40.

m.p.: 76.9-78.7 $^{o}$C.

$[\alpha]_D$ -0.9° (*c* 1.0, $CHCl_3$);

$^1$H NMR (500 MHz, $CDCl_3$) δ: 6.66 (1H, dd, *J* = 3.6, 1.7, H-6), 4.96-4.89 (1H, m, H-5), 4.67 (1H, t, *J* = 9.0, H-4), 4.62 (1H, ddd, *J* = 15.7, 2.9, 1.6, H-8), 4.36 (1H, dd, *J* = 8.9, 4.9, H-4), 4.02 (1H, ddd, *J* = 15.8, 4.7, 2.4, H-8), 2.38 (3H, s, H-10).

$^{13}$C NMR (125.7 MHz, $CDCl_3$) δ: 193.9 (C-9), 162.5 (C-2), 145.1 (C-7), 138.0 (C-6), 67.4 (C-4), 65.4 (C-5), 53.6 (C-8), 27.0 (C-10).

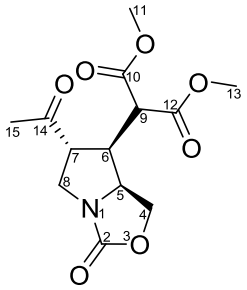
FTIR $\upsilon_{max}$ cm$^{-1}$(neat): 2922 (=C of enone), 1733 (C=O of oxazolidinone ring), 1671 (C=O of enone), 1185 (C-O), 1006 ( $H_3$C-N), 775.

HRMS (ESI+): *m/z* calculated for $C_8H_9NO_3Na$ $[M+Na]^+$ = 190.0475 found =190.0478.

Spectroscopic data identical to literature values.[96]

## 4.5. Formal synthesis of allokainic acid 2.2 and epikainate 2.346.

**Dimethyl 2-((6*R*,7*S*,7a*S*)-6-acetyl-3-oxohexahydropyrrolo[1,2-*c*]oxazol-7-yl)malonate 2.329**



To a suspension of sodium hydride (60 % dispersion in oil, 0.51 g, 8.5 mmol) in THF (40 mL), a solution of dimethyl malonate (1.12 g, 8.5 mmol) in THF (15 mL) was added. The reaction mixture was stirred at room temperature for 2 h, then a solution of (*S*)-6-acetyl-1,7a-dihydropyrrolo[1,2-*c*]oxazol-3(5*H*)-one **2.287**, (1.42 g, 8.5 mmol) in THF (15 mL) was added dropwise at 0 °C. The mixture was left to stir overnight at room temperature. The reaction was quenched with a saturated ammonium chloride solution (20 mL) and extracted with diethyl ether (5 x 30 mL). The combined organic phases were washed with brine (20 mL), dried over magnesium sulfate and the solvent was removed under reduced pressure. The resultant residue obtained was purified using flash column chromatography (hexanes/ethyl acetate : 7/3) to yield the dicarboxylates **2.329** and **2.328** as a mixture of two isomers in 1:1 ratio, as a pale yellow solid (2.33 g, 90 %). The X-Ray crystallographic studies confirmed the structure (figure 3.8).

TLC, (EtOAc) Rf = 0.88.

m.p.: 117.5-127.2 $^{o}$C

$[\alpha]_D$ -2.5° (*c* 1.0, $CHCl_3$);

$^1$H NMR (500 MHz, $CDCl_3$) δ: 4.53-4.47 (1H, m, H-5), 4.44-4.40 (1H, m, H-4), 4.33 (1H, dd, *J* = 11.7, 6.3, H-4), 4.04-3.99 (1H, m, H-9), 3.91 (1H, t, *J* = 8.4, H-8), 3.74

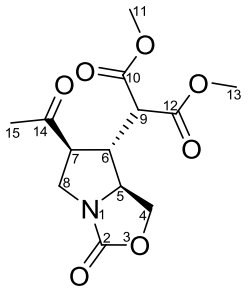
(6H, 2 x s, H-11 and H-13), 3.29 (1H, m, H-6), 3.26 (1H, m, H-8), 3.04 (1H, m, H-7), 2.21 (3H, s, H-15).

$^{13}$C NMR (125.7 MHz, $CDCl_3$) δ: 208.6 (C-14), 169.0 and 168.9 (C-10 and C-12), 161.3 (C-2), 65.5 (C-4), 58.1 (C-5), 53.0 and 52.9 (C-11 and C-13), 52.1 (C-6), 49.2 (C-8), 48.0 (C-9), 43.9 (C-7), 30.0 (C-15).

FTIR $\upsilon_{max}$ $cm^{-1}$(neat): 2929 ($CH_3$), 1732 (C=O of lactone), 1728 (C=O of ester) 1680 (C=O of ketone), 1436 ($CH_2$), 1248 (C-N), 1154, 767.

HRMS (ESI+): *m/z* calculated for $C_{13}H_{17}NO_7Na$ $[M+Na]^+$ = 322.0897 found = 322.0893.

**Dimethyl 2-((6*S*,7*R*,7a*S*)-6-acetyl-3-oxohexahydropyrrolo[1,2-*c*]oxazol-7-yl)malonate** 2.**328**




TLC, (EtOAc) Rf = 0.74.

m.p.: 118.3-128.3 $^oC$

$[\alpha]_D$ -0.9° (*c* 1.0, $CHCl_3$);

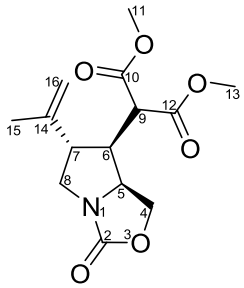
$^1$H NMR (500 MHz, $CDCl_3$) δ: 4.44-4.41 (1H, m, H-4), 4.41-4.38 (1H, m, H-5), 4.11-4.08 (1H, m, H-8), 4.07-4.02 (1H, m, H-4), 3.77 and 3.72 (6H, 2 x s, H-11 and H-13), 3.48-3.45 (1H, m, H-9), 3.38-3.33 (1H, m, H-6), 3.33-3.29 (1H, m, H-7), 3.06-3.01 (1H, m, H-8), 2.22 (3H, s, H-15).

$^{13}$C NMR (125.7 MHz, $CDCl_3$) δ: 205.6 (C-14), 168.5 and 168.2 (C-10 and C-12), 160.2 (C-2), 64.2 (C-4), 60.0 (C-5), 55.2 (C-7), 53.2 (C-11 and C-13), 51.3 (C-9), 48.3 (C-8), 42.2 (C-6), 29.9 (C-15).

FTIR $\upsilon_{max}$ $cm^{-1}$(neat): 2959 ($CH_3$), 1737 (C=O of lactone),1730 (C=O of ester) 1701 (C=O of ketone), 1432 ($CH_2$), 1273 (C-N), 1020, 769..

HRMS (ESI+): *m/z* calculated for $C_{13}H_{17}NO_7Na$ $[M+Na]^+$ = 322.0897 found = 322.0906.

**Dimethyl 2-((6*S*,7*S*,7a*S*)-3-oxo-6-(prop-1-en-2-yl)hexahydropyrrolo[1,2-*c*]oxazol-7-yl)malonate 2.343**




The olefination was performed by a modification of the procedure of Hanessian.[53]

*n*-BuLi in hexane (2.5 M, 2.84 mL) was added at -78 °C to a suspension of $Ph_3PMeBr$ (12.03 g, 33.6 mmol) in THF (30 mL). The mixture was stirred at room temperature for 20 min and then brought to -60 °C prior to the addition of a solution of dimethyl 2-((6*R*,7*S*,7a*S*)-6-acetyl-3-oxohexahydropyrrolo[1,2-*c*]oxazol-7-yl)malonate **2.329**, (0.85 g) in THF (20 mL). The reaction mixture was kept at -60 °C for 1 h and warmed to 25 °C over a period of 0.5 h. The reaction mixture was filtered over Celite®-silica gel, and the remaining solvent was removed under reduced pressure and the resulting residue was subjected to flash column chromatography on silica, eluting with (60% ethyl acetate in hexane) to afford **2.343** as a white solid (0.69 g, 81%).

TLC, (EtOAc/Hexane: 2/5) Rf = 0.70.

m.p.: 105.7-108.3 $^oC$

$[\alpha]_D$ -2.1° (*c* 1.0, $CHCl_3$);

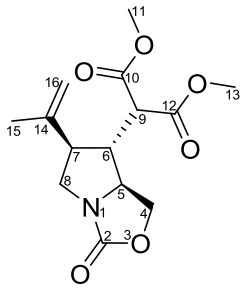
$^1$H NMR (500 MHz, $CDCl_3$) δ: 4.90-4.86 (1H, m, H-16), 4.81 (1H, s, H-16), 4.54 (1H, td, *J* = 8.8, 5.2, H-5), 4.41 (1H, dd, *J* = 9.9, 8.8, H-4), 3.94 (1H, dd, *J* = 10.0, 5.2, H-4), 3.87 (1H, dd, *J* = 12.0, 7.2, H-8), 3.76 and 3.65 (6H, 2 x s, H-11 and H-13), 3.40 (1H, d, *J* = 11.1 , H-9), 3.04-2.97 (1H, m, H-6), 2.97-2.91 (1H, m, H-8), 2.56 (1H, td, *J* = 9.9, 7.4, H-7), 1.71 (3H, s, H-15).

$^{13}$C NMR (125.7 MHz, $CDCl_3$) δ: 168.9 and 167.9 (C-10 and C-12), 160.9 (C-2), 141.1 (C-14), 114.5 (C-16), 64.9 (C-4), 60.0 (C-5), 53.1 and 52.4 (C-11 and C-13), 52.3 (C-9), 51.5 (C-7), 50.9 (C-8), 42.7 (C-6), 18.8 (C-15).

FTIR $\upsilon_{max}$ $cm^{-1}$(neat): 2962 ($CH_3$), 2929 (=$CH_2$), 2030 (C=C, alkene), 1728 ( -C=O- of lactone), 1690 ( C=O, ester), 1440 ($CH_2$), 1243 (C-N), 1150, 1008, 923.

HRMS (ESI+): *m/z* calculated for $C_{14}H_{19}NO_6Na$ $[M+Na]^+$ = 320.1105 found = 320.1102.

**Dimethyl 2-((6*R*,7*R*,7a*S*)-3-oxo-6-(prop-1-en-2-yl)hexahydropyrrolo[1,2-*c*]oxazol-7-yl)malonate** 2.**338**




The olefination was performed by a modification of the procedure of Hanessian.[53]

*n*-BuLi in hexane (2.5 M, 2.84 mL) was added at -78 °C to a suspension of $Ph_3PMeBr$ (12.03 g, 33.6 mmol) in THF (30 mL). The mixture was stirred at room temperature for 20 min and then brought to -60 °C prior to the addition of a solution of dimethyl 2-((6*S*,7*R*,7a*S*)-6-acetyl-3-oxohexahydropyrrolo[1,2-*c*]oxazol-7-yl)malonate **2.328**, (0.85 g) in THF (20 mL). The reaction mixture was kept at -60 °C for 1 h and warmed to 25

°C over a period of 0.5 h. The reaction mixture was filtered over Celite-silica gel, and the remaining solvent was removed under reduced pressure. The residue obtained was subjected to flash column chromatography on silica, eluting with (60% ethyl acetate in hexane) to afford **2.338** as a white solid (0.61 g, 72%). The compound **2.329** was formed as byproduct (0.07 g, 10%).

TLC, (EtOAc/Hexane: 2/5) Rf = 0.65.

m.p.: 106.5-109.8 $^{o}$C

$[\alpha]_D$ -1.28 ° (*c* 1.0, $CHCl_3$);

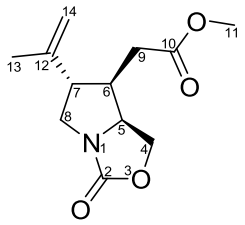
$^1$H NMR (500 MHz, $CDCl_3$) δ: 4.85-4.82 (1H, m, H-16), 4.81 (1H, s, H-16), 4.51 (1H, dd, *J* = 9.5, 8.0, H-4), 4.45-4.40 (1H, m, H-4), 4.05 (1H, td, *J* = 8.5, 4.3, H-5), 3.75-3.69 (6H, 2 x s, H-11 and H-13), 3.54-3.49 (1H, m, H-8), 3.49-3.46 (1H, m, H-9), 3.37 (1H, dd, *J* = 11.6, 9.4, H-8), 2.96 (1H, dd, *J* = 17.1, 9.4, H-6), 2.43 (1H, dt, *J* = 16.8, 8.5, H-7), 1.68 (3H, s, H-15).

$^{13}$C NMR (125.7 MHz, $CDCl_3$) δ: 168.1 (C-10 and C-12), 160.3 (C-2), 141.8 (C-14), 114.7 (C-16), 68.2 (C-4), 62.2 (C-5), 53.2 (C-6),52.8 and 52.5 (C-11 and C-13), 52.3 (C-9), 48.5 (C-8), 45.8 (C-7), 17.7 (C-15).

FTIR $\upsilon_{max}$ $cm^{-1}$(neat): 2956 ($CH_3$), 2929 (=$CH_2$), 2163 (C=C), 1728 (C=O of lactone), 1645 (C=O of ester), 1435 ($CH_2$), 1225 (C-N), 1157, 1005, 902.

HRMS (ESI+): *m/z* calculated for $C_{14}H_{19}NO_6Na$ $[M+Na]^+$ = 320.1105 found = 320.1101.

**Methyl 2-((6*S*,7*R*,7a*S*)-3-oxo-6-(prop-1-en-2-yl)hexahydropyrrolo[1,2-*c*]oxazol-7-yl)acetate 2.345**




The decarboxylation was performed by a modification of the procedure of Krapcho.[124]

29 mg of NaCl (0.50 mmol) was added to 150 mg (0.46 mmol) of dimethyl 2-((6*S*,7*S*,7a*S*)-3-oxo-6-(prop-1-en-2-yl)hexahydropyrrolo[1,2-*c*]oxazol-7-yl)malonate 2.**343** in 12 mL of hydrated DMSO and heated to 170 $^{o}$C for 8 hours. After cooling down to room temperature, the organic layer was extracted with ethyl acetate (3 x 15 mL) and dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue obtained was subjected to flash column chromatography on silica, eluting with (EtOAc/hexane, 2:8) to give **2.345** as orange oil (72 mg, 75%).

TLC, (EtOAc/Hexane: 1/5) Rf = 0.38.

$[\alpha]_D$ +3.2° (*c* 1.0, $CHCl_3$);

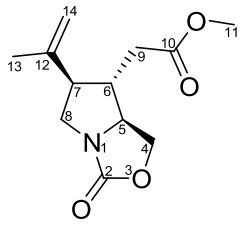
$^1$H NMR (500 MHz, $CDCl_3$) δ: 4.94-4.91 (1H, m, H-14), 4.83 (1H, d, *J* =8.9 Hz, H-14), 4.45 (1H, dt, *J* = 14.6, 7.3 Hz, H-4), 4.36 (1H, td, *J* = 8.3, 5.1 Hz, H-5), 4.12 (1H, dd, *J* = 9.6, 5.1 Hz, H-4), 3.85 (1H, dd, *J* = 11.9, 7.2 Hz, H-8), 3.70 (3H, s, H-11), 3.04-2.97 (1H, dd, *J* = 11.9, 8.9 Hz, H-8), 2.64-2.55 (1H, m, H-7), 2.48 (1H, dd, *J* = 16.9, 5.6 Hz, H-9), 2.36 (1H, d, *J* = 6.5 Hz, H-6), 2.35-2.31 (1H, m, H-9), 1.76 (3H, s, H-13).

$^{13}$C NMR (125.7 MHz, $CDCl_3$) δ: 172.4 (C-10), 161.5 (C-2), 142.0 (C-12), 113.4 (C-14), 64.7 (C-4), 59.6 (C-5), 52.8 (C-7), 52.0 (C-11), 50.1 (C-8), 40.5 (C-6), 33.3 (C-9), 20.2 (C-13).

FTIR $\upsilon_{max}$ $cm^{-1}$(neat): 2945 ($CH_3$), 2920 (=$CH_2$), 1730 (C=O of lactone), 1645 (C=O of ester), 1437 ($CH_2$), 1378 ($CH_2$), 1207 (C-N), 1169, 1013, 895.

HRMS (ESI+): *m/z* calculated for $C_{12}H_{17}NO_4Na$ $[M+Na]^+$ = 262.1050 found = 262.1052.

**Methyl 2-((6*R*,7*S*,7a*S*)-3-oxo-6-(prop-1-en-2-yl)hexahydropyrrolo[1,2-*c*]oxazol-7-yl)acetate 2.233**




The decarboxylation was performed by a modification of the procedure of Krapcho.[124]

29 mg of NaCl (0.50 mmol) was added to 150 mg (0.46 mmol) of dimethyl 2-((6*R*,7*R*,7a*S*)-3-oxo-6-(prop-1-en-2-yl)hexahydropyrrolo[1,2-*c*]oxazol-7-yl)malonate 2.**338** in 12 mL of hydrated DMSO and heated to 170 $^oC$ for 8 hours. After cooling down to room temperature, the organic layer was extracted with ethyl acetate (3 x 15 mL) and dried over magnesium sulfate, filtered and concentrated under reduced pressure. The resulting residue was subjected to flash column chromatography on silica, eluting with (EtOAc/hexane, 2:8) to give **2.333** as orange oil (80 mg, 83%).

TLC, (EtOAc/Hexane: 1/5) Rf = 0.37.

$[\alpha]_D$ +5.2° (*c* 1.0, $CHCl_3$);

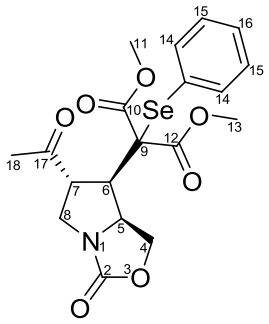
$^1$H NMR (500 MHz, $CDCl_3$) δ: 4.89 (1H, dd, *J* = 2.9, 1.4 Hz, H-14), 4.87-4.85 (1H, m, H-14), 4.52 (1H, dd, *J* = 9.4, 7.9 Hz, H-4), 4.41 (1H, dd, *J* = 9.4, 4.2 Hz, H-4), 3.78 (1H, ddd, *J* = 9.2, 8.0, 4.2 Hz, H-5), 3.68 (3H, s, H-11), 3.47 (1H, dd, *J* = 11.4, 8.9 Hz, H-8), 3.43-3.37 (1H, m, H-8), 2.73 (1H, dd, *J* = 19.7, 9.2 Hz, H-7), 2.58 (1H, dd, *J* = 15.9, 3.7 Hz, H-9), 2.25-2.18 (1H, m, H-9), 2.12 (1H, ddd, *J* = 20.3, 9.7, 3.7 Hz, H-6), 1.71 (3H, s, H-13).

$^{13}$C NMR (125.7 MHz, $CDCl_3$) δ: 172.2 (C-10), 160.7 (C-2), 141.2 (C-12), 114.7 (C-14), 67.7 (C-4), 64.7 (C-5), 55.0 (C-7), 51.8 (C-11), 48.7 (C-8), 43.3 (C-6), 34.9 (C-9), 18.1 (C-13).

FTIR $\upsilon_{max}$ $cm^{-1}$(neat): 2953 ($CH_3$), 2918 (=$CH_2$), 1730 (C=O of lactone), 1644 (C=O of ester), 1437 ($CH_2$), 1394 ($CH_2$), 1206 (C-N), 1166, 1002, 897.

HRMS (ESI): *m/z* calculated for $C_{12}H_{17}NO_4$ $[M+Na]^+$ 262.1050 found 262.1048.

**Dimethyl 2-((6*S*,7*S*,7*aS*)-6-acetyl-3-oxohexahydropyrrolo[1,2-c]oxazol-7-yl)-2-(phenylselanyl)malonate 2.352**




The selenation was performed by the modification of the procedure of Rubio.[59]

To a solution of 100 mg (0.31 mmol) dimethyl 2-((6*R*,7*S*,7a*S*)-6-acetyl-3-oxohexahydropyrrolo[1,2-*c*]oxazol-7-yl)malonate **2.329**, in Anhydrous THF 10 mL, was added a 1M solution of KHMDS (0.35 mL, 1.0 mmol) at 0 $^oC$. After 30 min a solution of phenylselenyl chloride (45 mg, 1.09 mmol) in 5 mL of THF was added at 0 $^oC$. The mixture was stirred overnight at room temperature. The reaction was quenched with saturated ammonium chloride solution (10 mL) and extracted with diethyl ether (3 x 15 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was subjected to flash column chromatography on silica, eluting with (EtOAc/hexane, 1:6) to give the selenated compound **2.352** as a red semi-solid (118 mg, 78%).

TLC, (EtOAc/hexane 2/5) Rf = 0.42.

$[\alpha]_D$ -3.2° (*c* 1.0, $CHCl_3$);

$^1$H NMR (500 MHz, $CDCl_3$) δ: 7.54 (2H, m, H-14), 7.47 (1H, m, H-16), 7.38 (2H, m, H-15), 4.46-4.37 (2H, m, H-4), 4.35 (1H, dd, *J* = 12.0, 3.4, H-5), 4.08 (1H, m, H-8), 3.83-3.71 (6H, m, H-11 and H-13), 3.70 (1H, m, H-7), 3.67 (1H, m, H-6), 2.96 (1H, dt, *J* = 12.7, 6.4, H-8), 2.26 (3H, m, H-18).

$^{13}$C NMR (125.7 MHz, $CDCl_3$) δ: 207.0 (C-17), 168.4 (C-10 and C-12), 159.5 (C-2), 154.2 (C-9), 137.91 (C-14), 130.6 (C-15), 129.3 (C-16), 64.9 (C-4), 60.8 (C-5), 55.5 (C-7), 53.9 (C-11 and C-13), 53.2 (C-6), 47.8 (C-8), 30.4 (C-15).

FTIR $\upsilon_{max}$ $cm^{-1}$(neat): 2982 ($CH_3$), 1673 (C=O of ester).

HRMS (ESI): *m/z* calculated for $C_{19}H_{21}NO_7Se$ $[M+Na]^+$ 478.0375 found 478.0375.

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# 6. Appendices

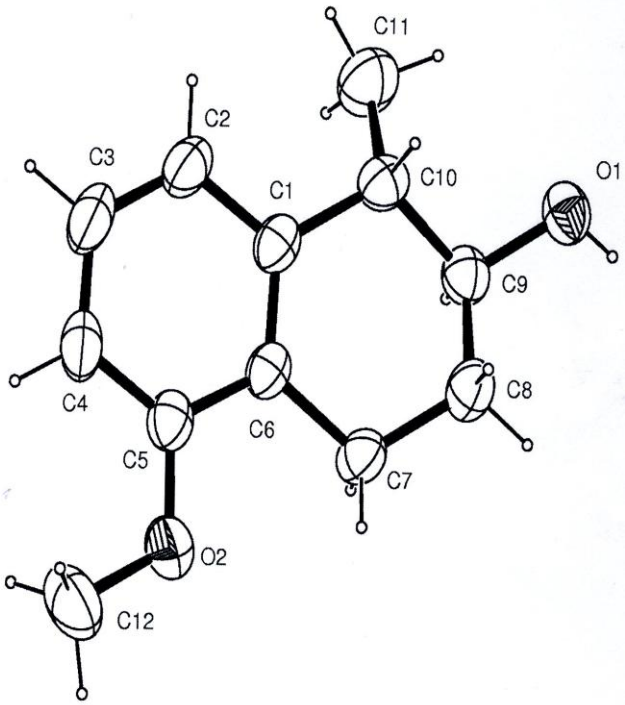
C11
C2
C3
C1
C10
O1
C9
C4
C6
C8
C5
C7
O2
C12

Table 1. Crystal data and structure refinement

| | | |
|---|---|---|
| Identification code | apr1908 | |
| Empirical formula | C12 H16 O2 | |
| Formula weight | 192.25 | |
| Temperature | 173(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Tetragonal | |
| Space group | $I4_1/a$ (No.88) | |
| Unit cell dimensions | a = 23.4917(8) Å | $\alpha$= 90°. |
| | b = 23.4917(8) Å | $\beta$= 90°. |
| | c = 7.6608(4) Å | $\gamma$ = 90°. |
| Volume | 4227.7(3) $Å^3$ | |
| Z | 16 | |
| Density (calculated) | 1.21 $Mg/m^3$ | |
| Absorption coefficient | 0.08 $mm^{-1}$ | |
| F(000) | 1664 | |
| Crystal size | 0.4 x 0.4 x 0.4 $mm^3$ | |
| Theta range for data collection | 3.47 to 26.01°. | |
| Index ranges | -25<=h<=28, -24<=k<=28, -6<=l<=9 | |
| Reflections collected | 8346 | |
| Independent reflections | 2047 [R(int) = 0.121] | |
| Reflections with I>2sigma(I) | 1710 | |
| Completeness to theta = 26.01° | 98.2 % | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 2047 / 0 / 133 | |
| Goodness-of-fit on $F^2$ | 1.034 | |
| Final R indices [I>2sigma(I)] | R1 = 0.073, wR2 = 0.199 | |
| R indices (all data) | R1 = 0.085, wR2 = 0.209 | |
| Largest diff. peak and hole | 0.35 and -0.18 $e.Å^{-3}$ | |

Data collection KappaCCD , Program package WinGX , Abs correction not applied ,
Refinement using SHELXL-97 , Drawing using ORTEP-3 for Windows

Table 2. Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters ($Å^2$x $10^3$) for apr1908. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| O(1) | 2418(1) | 5569(1) | 5848(3) | 42(1) |
| O(2) | 3789(1) | 7549(1) | 9619(2) | 49(1) |
| C(1) | 3139(1) | 6983(1) | 5692(3) | 37(1) |
| C(2) | 3314(1) | 7387(1) | 4445(4) | 48(1) |
| C(3) | 3647(1) | 7846(1) | 4950(4) | 54(1) |
| C(4) | 3817(1) | 7916(1) | 6663(4) | 48(1) |
| C(5) | 3642(1) | 7520(1) | 7889(3) | 40(1) |
| C(6) | 3296(1) | 7054(1) | 7427(3) | 34(1) |
| C(7) | 3112(1) | 6638(1) | 8827(3) | 41(1) |
| C(8) | 2978(1) | 6054(1) | 8059(4) | 45(1) |
| C(9) | 2572(1) | 6110(1) | 6561(3) | 41(1) |
| C(10) | 2813(1) | 6457(1) | 5066(3) | 41(1) |
| C(11) | 2356(1) | 6592(1) | 3740(4) | 63(1) |
| C(12) | 4169(1) | 7993(1) | 10116(5) | 64(1) |

Table 3. Bond lengths [Å] and angles [°] for apr1908.

| | |
|---|---|
| O(1)-C(9) | 1.429(3) |
| O(2)-C(5) | 1.371(3) |
| O(2)-C(12) | 1.425(3) |
| C(1)-C(6) | 1.389(3) |
| C(1)-C(2) | 1.409(3) |
| C(1)-C(10) | 1.530(3) |
| C(2)-C(3) | 1.387(4) |
| C(3)-C(4) | 1.382(4) |
| C(4)-C(5) | 1.384(3) |
| C(5)-C(6) | 1.410(3) |
| C(6)-C(7) | 1.513(3) |
| C(7)-C(8) | 1.526(4) |
| C(8)-C(9) | 1.498(4) |
| C(9)-C(10) | 1.516(3) |
| C(10)-C(11) | 1.512(4) |
| | |
| C(5)-O(2)-C(12) | 116.9(2) |
| C(6)-C(1)-C(2) | 119.4(2) |
| C(6)-C(1)-C(10) | 122.0(2) |
| C(2)-C(1)-C(10) | 118.5(2) |
| C(3)-C(2)-C(1) | 120.0(3) |
| C(4)-C(3)-C(2) | 121.3(2) |
| C(3)-C(4)-C(5) | 118.6(2) |
| O(2)-C(5)-C(4) | 123.2(2) |
| O(2)-C(5)-C(6) | 115.2(2) |
| C(4)-C(5)-C(6) | 121.6(2) |
| C(1)-C(6)-C(5) | 119.1(2) |
| C(1)-C(6)-C(7) | 121.7(2) |
| C(5)-C(6)-C(7) | 119.2(2) |
| C(6)-C(7)-C(8) | 111.4(2) |
| C(9)-C(8)-C(7) | 110.3(2) |
| O(1)-C(9)-C(8) | 112.1(2) |
| O(1)-C(9)-C(10) | 106.5(2) |
| C(8)-C(9)-C(10) | 112.8(2) |
| C(11)-C(10)-C(9) | 110.8(2) |
| C(11)-C(10)-C(1) | 113.4(2) |

| | |
|---|---|
| C(9)-C(10)-C(1) | 112.6(2) |

Hydrogen bonds with H..A < r(A) + 2.000 Angstroms and <DHA > 110 deg.

| D-H | d(D-H) | d(H..A) | <DHA | d(D..A) | A |
|---|---|---|---|---|---|
| O1-H1X | 0.79 | 1.92 | 176 | 2.705 | O1 [ -y+3/4, x+1/4, z+1/4 ] |

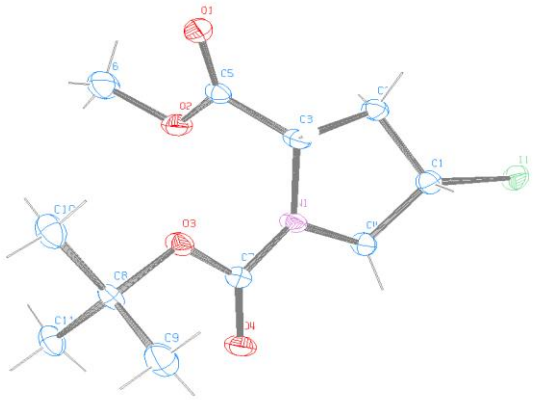

Table 1. Crystal data and structure refinement for import.

| | |
|---|---|
| Identification code | shelxl |
| Empirical formula | C11 H18 I N O4 |
| Formula weight | 355.16 |
| Temperature | 173(2) K |
| Wavelength | 0.71073 A |

| | |
|---|---|
| Crystal system, space group | monoclinic, P 21 |
| Unit cell dimensions | a = 5.6368(3) A alpha = 90 deg.<br>b = 9.1663(4) A beta = 98.970(2) deg.<br>c = 13.8464(7) A gamma = 90 deg. |
| Volume | 706.67(6) A^3 |
| Z, Calculated density | 2, 1.669 Mg/m^3 |
| Absorption coefficient | 2.269 mm^-1 |
| F(000) | 352 |
| Crystal size | 0.25 x 0.12 x 0.08 mm |
| Theta range for data collection | 1.49 to 27.42 deg. |
| Limiting indices | -7<=h<=7, -9<=k<=11, -17<=l<=12 |
| Reflections collected / unique | 4203 / 2869 [R(int) = 0.0474] |
| Completeness to theta = 27.42 | 98.5 % |
| Max. and min. transmission | 0.8393 and 0.6008 |
| Refinement method | Full-matrix least-squares on F^2 |
| Data / restraints / parameters | 2869 / 1 / 154 |
| Goodness-of-fit on F^2 | 1.219 |

Final R indices [I>2sigma(I)] R1 = 0.0267, wR2 = 0.0841

R indices (all data) R1 = 0.0321, wR2 = 0.0975

Absolute structure parameter 0.01(3)

Largest diff. peak and hole 0.783 and -1.181 e.A^-3

Table 2. Atomic coordinates ( x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for import.
U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| C(1) | 9354(8) | 9597(5) | 7788(4) | 31(1) |
| C(2) | 9223(8) | 10864(6) | 8493(3) | 29(1) |
| C(3) | 10255(7) | 12135(5) | 7955(3) | 27(1) |
| C(4) | 11805(8) | 9807(5) | 7463(4) | 28(1) |
| C(5) | 11415(7) | 13253(5) | 8666(3) | 26(1) |
| C(6) | 14949(10) | 14137(9) | 9614(5) | 55(2) |
| C(7) | 13039(8) | 12050(5) | 6715(4) | 28(1) |
| C(8) | 13460(7) | 14449(5) | 5955(3) | 26(1) |

| | | | | |
|---|---|---|---|---|
| C(9) | 12236(9) | 14001(8) | 4950(4) | 42(1) |
| C(10) | 12646(9) | 15955(6) | 6225(5) | 39(1) |
| C(11) | 16199(7) | 14416(6) | 6052(4) | 34(1) |
| I(1) | 9083(1) | 7460(1) | 8401(1) | 40(1) |
| N(1) | 11893(7) | 11394(4) | 7383(3) | 29(1) |
| O(1) | 10303(6) | 14223(4) | 8969(3) | 40(1) |
| O(2) | 13762(6) | 13032(4) | 8951(3) | 38(1) |
| O(3) | 12615(6) | 13495(4) | 6701(3) | 29(1) |
| O(4) | 14300(7) | 11393(4) | 6219(3) | 39(1) |

Table 3. Bond lengths [A] and angles [deg] for import.

| | |
|---|---|
| C(1)-C(2) | 1.526(7) |
| C(1)-C(4) | 1.530(6) |
| C(1)-I(1) | 2.150(5) |
| C(1)-H(1) | 1.0000 |
| C(2)-C(3) | 1.544(6) |
| C(2)-H(2A) | 0.9900 |
| C(2)-H(2B) | 0.9900 |
| C(3)-N(1) | 1.472(5) |
| C(3)-C(5) | 1.499(7) |
| C(3)-H(3) | 1.0000 |
| C(4)-N(1) | 1.461(6) |

| | |
|---|---|
| C(4)-H(4A) | 0.9900 |
| C(4)-H(4B) | 0.9900 |
| C(5)-O(1) | 1.200(6) |
| C(5)-O(2) | 1.336(5) |
| C(6)-O(2) | 1.457(7) |
| C(6)-H(6A) | 0.9800 |
| C(6)-H(6B) | 0.9800 |
| C(6)-H(6C) | 0.9800 |
| C(7)-O(4) | 1.221(6) |
| C(7)-O(3) | 1.346(7) |
| C(7)-N(1) | 1.350(6) |
| C(8)-O(3) | 1.486(5) |
| C(8)-C(9) | 1.511(7) |
| C(8)-C(10) | 1.520(7) |
| C(8)-C(11) | 1.529(5) |
| C(9)-H(9A) | 0.9800 |
| C(9)-H(9B) | 0.9800 |
| C(9)-H(9C) | 0.9800 |
| C(10)-H(10A) | 0.9800 |
| C(10)-H(10B) | 0.9800 |
| C(10)-H(10C) | 0.9800 |
| C(11)-H(11A) | 0.9800 |
| C(11)-H(11B) | 0.9800 |
| C(11)-H(11C) | 0.9800 |

| | |
|---|---|
| C(2)-C(1)-C(4) | 103.2(4) |
| C(2)-C(1)-I(1) | 115.3(3) |
| C(4)-C(1)-I(1) | 110.7(3) |
| C(2)-C(1)-H(1) | 109.2 |
| C(4)-C(1)-H(1) | 109.2 |
| I(1)-C(1)-H(1) | 109.2 |
| C(1)-C(2)-C(3) | 101.9(3) |
| C(1)-C(2)-H(2A) | 111.4 |
| C(3)-C(2)-H(2A) | 111.4 |
| C(1)-C(2)-H(2B) | 111.4 |
| C(3)-C(2)-H(2B) | 111.4 |
| H(2A)-C(2)-H(2B) | 109.3 |
| N(1)-C(3)-C(5) | 115.0(3) |
| N(1)-C(3)-C(2) | 103.1(3) |
| C(5)-C(3)-C(2) | 111.0(4) |
| N(1)-C(3)-H(3) | 109.2 |
| C(5)-C(3)-H(3) | 109.2 |
| C(2)-C(3)-H(3) | 109.2 |
| N(1)-C(4)-C(1) | 101.0(4) |
| N(1)-C(4)-H(4A) | 111.6 |
| C(1)-C(4)-H(4A) | 111.6 |
| N(1)-C(4)-H(4B) | 111.6 |
| C(1)-C(4)-H(4B) | 111.6 |

| | |
|---|---|
| H(4A)-C(4)-H(4B) | 109.4 |
| O(1)-C(5)-O(2) | 123.8(5) |
| O(1)-C(5)-C(3) | 122.6(4) |
| O(2)-C(5)-C(3) | 113.6(4) |
| O(2)-C(6)-H(6A) | 109.5 |
| O(2)-C(6)-H(6B) | 109.5 |
| H(6A)-C(6)-H(6B) | 109.5 |
| O(2)-C(6)-H(6C) | 109.5 |
| H(6A)-C(6)-H(6C) | 109.5 |
| H(6B)-C(6)-H(6C) | 109.5 |
| O(4)-C(7)-O(3) | 126.5(4) |
| O(4)-C(7)-N(1) | 123.3(4) |
| O(3)-C(7)-N(1) | 110.2(4) |
| O(3)-C(8)-C(9) | 109.3(4) |
| O(3)-C(8)-C(10) | 102.9(3) |
| C(9)-C(8)-C(10) | 111.1(4) |
| O(3)-C(8)-C(11) | 110.9(3) |
| C(9)-C(8)-C(11) | 112.7(4) |
| C(10)-C(8)-C(11) | 109.6(4) |
| C(8)-C(9)-H(9A) | 109.5 |
| C(8)-C(9)-H(9B) | 109.5 |
| H(9A)-C(9)-H(9B) | 109.5 |
| C(8)-C(9)-H(9C) | 109.5 |
| H(9A)-C(9)-H(9C) | 109.5 |

| | |
|---|---|
| H(9B)-C(9)-H(9C) | 109.5 |
| C(8)-C(10)-H(10A) | 109.5 |
| C(8)-C(10)-H(10B) | 109.5 |
| H(10A)-C(10)-H(10B) | 109.5 |
| C(8)-C(10)-H(10C) | 109.5 |
| H(10A)-C(10)-H(10C) | 109.5 |
| H(10B)-C(10)-H(10C) | 109.5 |
| C(8)-C(11)-H(11A) | 109.5 |
| C(8)-C(11)-H(11B) | 109.5 |
| H(11A)-C(11)-H(11B) | 109.5 |
| C(8)-C(11)-H(11C) | 109.5 |
| H(11A)-C(11)-H(11C) | 109.5 |
| H(11B)-C(11)-H(11C) | 109.5 |
| C(7)-N(1)-C(4) | 121.4(4) |
| C(7)-N(1)-C(3) | 124.8(4) |
| C(4)-N(1)-C(3) | 112.8(3) |
| C(5)-O(2)-C(6) | 114.6(4) |
| C(7)-O(3)-C(8) | 120.9(4) |

---

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for import.

The anisotropic displacement factor exponent takes the form:

-2 pi^2 [ h^2 a*^2 U11 + ... + 2 h k a* b* U12 ]

| | U11 | U22 | U33 | U23 | U13 | U12 |
|---|---|---|---|---|---|---|
| C(1) | 36(2) | 28(3) | 30(2) | 2(2) | 10(2) | -2(2) |
| C(2) | 36(2) | 28(3) | 26(3) | 1(2) | 12(2) | 0(2) |
| C(3) | 27(2) | 26(3) | 30(2) | 3(2) | 15(2) | 5(2) |
| C(4) | 36(2) | 19(2) | 32(2) | 6(2) | 11(2) | 3(2) |
| C(5) | 30(2) | 23(2) | 28(2) | 6(2) | 13(2) | 4(2) |
| C(6) | 38(2) | 79(5) | 49(3) | -20(3) | 12(2) | -18(3) |
| C(7) | 29(2) | 30(3) | 25(2) | -1(2) | 9(2) | -1(2) |
| C(8) | 21(2) | 32(3) | 25(2) | 8(2) | 6(2) | -3(2) |
| C(9) | 37(2) | 59(4) | 29(2) | 6(3) | 1(2) | -12(2) |
| C(10) | 35(2) | 30(3) | 52(3) | 13(2) | 10(2) | 2(2) |
| C(11) | 23(2) | 33(3) | 47(3) | 6(2) | 8(2) | -1(2) |
| I(1) | 60(1) | 24(1) | 39(1) | -1(1) | 18(1) | -10(1) |
| N(1) | 39(2) | 21(2) | 31(2) | 4(2) | 19(2) | 3(2) |
| O(1) | 41(2) | 27(2) | 56(2) | -6(2) | 21(2) | 1(2) |
| O(2) | 32(2) | 47(2) | 36(2) | -10(2) | 11(1) | 2(1) |
| O(3) | 35(2) | 24(2) | 30(2) | 5(2) | 13(1) | 3(1) |

| | | | | | | |
|---|---|---|---|---|---|---|
| O(4) | 52(2) | 32(2) | 38(2) | 0(2) | 26(2) | 3(2) |

Table 5. Torsion angles [deg] for import.

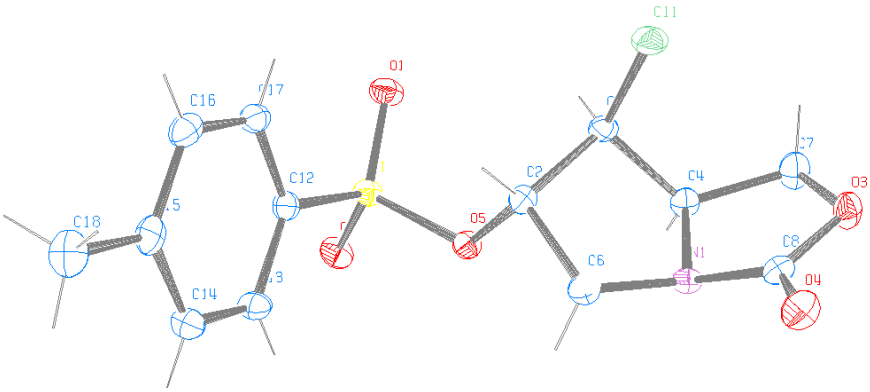


Table 1. Crystal data and structure refinement for import.

| | |
|---|---|
| Identification code | shelxl |
| Empirical formula | C13 H14 Cl N O5 S |
| Formula weight | 331.76 |
| Temperature | 173(2) K |
| Wavelength | 0.71073 A |
| Crystal system, space group | monoclinic, P21/c |

| | |
|---|---|
| Unit cell dimensions | a = 11.4168(2) A alpha = 90 deg.<br>b = 6.24090(10) A beta = 103.7490(10) deg.<br>c = 20.3795(4) A gamma = 90 deg. |
| Volume | 1410.45(4) A^3 |
| Z, Calculated density | 4, 1.562 Mg/m^3 |
| Absorption coefficient | 0.440 mm^-1 |
| F(000) | 688 |
| Crystal size | 0.30 x 0.20 x 0.15 mm |
| Theta range for data collection | 3.42 to 27.87 deg. |
| Limiting indices | -14<=h<=14, -7<=k<=8, -25<=l<=26 |
| Reflections collected / unique | 18724 / 3176 [R(int) = 0.0656] |
| Completeness to theta = 27.87 | 94.6 % |
| Max. and min. transmission | 0.9370 and 0.8794 |
| Refinement method | Full-matrix least-squares on F^2 |
| Data / restraints / parameters | 3176 / 0 / 190 |
| Goodness-of-fit on F^2 | 1.226 |
| Final R indices [I>2sigma(I)] | R1 = 0.0646, wR2 = 0.1964 |

| | |
|---|---|
| R indices (all data) | R1 = 0.0761, wR2 = 0.2021 |
| Largest diff. peak and hole | 0.630 and -0.456 e.A^-3 |

Table 2. Atomic coordinates ( x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for import.
U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| O(5) | 10292(3) | 2226(5) | 4355(1) | 24(1) |
| C(2) | 9855(4) | 1341(6) | 3677(2) | 22(1) |
| C(3) | 8897(4) | 2812(6) | 3261(2) | 24(1) |
| C(4) | 7778(4) | 2207(6) | 3508(2) | 23(1) |
| C(6) | 9190(4) | -745(7) | 3758(2) | 26(1) |
| C(7) | 6526(4) | 2379(7) | 3040(3) | 34(1) |
| C(8) | 7107(4) | -1160(7) | 3100(2) | 26(1) |
| C(12) | 12562(4) | 1768(7) | 4354(2) | 24(1) |
| C(13) | 12848(4) | 53(8) | 4797(2) | 30(1) |
| C(14) | 13632(4) | -1500(8) | 4682(2) | 32(1) |
| C(15) | 14141(4) | -1384(8) | 4122(2) | 30(1) |
| C(16) | 13848(4) | 359(8) | 3687(2) | 30(1) |
| C(17) | 13054(4) | 1935(7) | 3795(2) | 27(1) |
| C(18) | 14970(4) | -3106(9) | 3987(3) | 39(1) |

| | | | | |
|---|---|---|---|---|
| Cl(1) | 8723(1) | 2102(2) | 2391(1) | 34(1) |
| N(1) | 7916(3) | -116(5) | 3608(2) | 21(1) |
| O(1) | 11344(3) | 5272(5) | 3980(2) | 33(1) |
| O(2) | 11705(3) | 4173(5) | 5180(2) | 33(1) |
| O(3) | 6225(3) | 209(5) | 2793(2) | 31(1) |
| O(4) | 7128(3) | -3007(5) | 2940(2) | 35(1) |
| S(1) | 11487(1) | 3636(2) | 4483(1) | 24(1) |

Table 3. Bond lengths [A] and angles [deg] for import.

| | |
|---|---|
| O(5)-C(2) | 1.462(4) |
| O(5)-S(1) | 1.592(3) |
| C(2)-C(3) | 1.522(6) |
| C(2)-C(6) | 1.536(6) |
| C(2)-H(2) | 1.0000 |
| C(3)-C(4) | 1.527(6) |
| C(3)-Cl(1) | 1.793(4) |
| C(3)-H(3) | 1.0000 |
| C(4)-N(1) | 1.467(5) |
| C(4)-C(7) | 1.521(6) |
| C(4)-H(4) | 1.0000 |
| C(6)-N(1) | 1.467(5) |

| | |
|---|---|
| C(6)-H(6A) | 0.9900 |
| C(6)-H(6B) | 0.9900 |
| C(7)-O(3) | 1.457(5) |
| C(7)-H(7A) | 0.9900 |
| C(7)-H(7B) | 0.9900 |
| C(8)-O(4) | 1.199(5) |
| C(8)-O(3) | 1.354(5) |
| C(8)-N(1) | 1.377(5) |
| C(12)-C(13) | 1.387(6) |
| C(12)-C(17) | 1.389(6) |
| C(12)-S(1) | 1.756(4) |
| C(13)-C(14) | 1.376(7) |
| C(13)-H(13) | 0.9500 |
| C(14)-C(15) | 1.401(6) |
| C(14)-H(14) | 0.9500 |
| C(15)-C(16) | 1.393(7) |
| C(15)-C(18) | 1.500(7) |
| C(16)-C(17) | 1.390(6) |
| C(16)-H(16) | 0.9500 |
| C(17)-H(17) | 0.9500 |
| C(18)-H(18A) | 0.9800 |
| C(18)-H(18B) | 0.9800 |
| C(18)-H(18C) | 0.9800 |
| O(1)-S(1) | 1.429(3) |

| | |
|---|---|
| O(2)-S(1) | 1.423(3) |
| | |
| C(2)-O(5)-S(1) | 116.7(2) |
| O(5)-C(2)-C(3) | 109.6(3) |
| O(5)-C(2)-C(6) | 106.5(3) |
| C(3)-C(2)-C(6) | 105.2(3) |
| O(5)-C(2)-H(2) | 111.7 |
| C(3)-C(2)-H(2) | 111.7 |
| C(6)-C(2)-H(2) | 111.7 |
| C(2)-C(3)-C(4) | 102.4(3) |
| C(2)-C(3)-Cl(1) | 107.3(3) |
| C(4)-C(3)-Cl(1) | 111.1(3) |
| C(2)-C(3)-H(3) | 111.9 |
| C(4)-C(3)-H(3) | 111.9 |
| Cl(1)-C(3)-H(3) | 111.9 |
| N(1)-C(4)-C(7) | 102.2(3) |
| N(1)-C(4)-C(3) | 102.7(3) |
| C(7)-C(4)-C(3) | 120.8(4) |
| N(1)-C(4)-H(4) | 110.1 |
| C(7)-C(4)-H(4) | 110.1 |
| C(3)-C(4)-H(4) | 110.1 |
| N(1)-C(6)-C(2) | 104.0(3) |
| N(1)-C(6)-H(6A) | 111.0 |
| C(2)-C(6)-H(6A) | 111.0 |

| | |
|---|---|
| N(1)-C(6)-H(6B) | 111.0 |
| C(2)-C(6)-H(6B) | 111.0 |
| H(6A)-C(6)-H(6B) | 109.0 |
| O(3)-C(7)-C(4) | 105.1(3) |
| O(3)-C(7)-H(7A) | 110.7 |
| C(4)-C(7)-H(7A) | 110.7 |
| O(3)-C(7)-H(7B) | 110.7 |
| C(4)-C(7)-H(7B) | 110.7 |
| H(7A)-C(7)-H(7B) | 108.8 |
| O(4)-C(8)-O(3) | 122.8(4) |
| O(4)-C(8)-N(1) | 127.3(4) |
| O(3)-C(8)-N(1) | 109.9(3) |
| C(13)-C(12)-C(17) | 120.8(4) |
| C(13)-C(12)-S(1) | 118.7(3) |
| C(17)-C(12)-S(1) | 120.3(3) |
| C(14)-C(13)-C(12) | 119.7(4) |
| C(14)-C(13)-H(13) | 120.2 |
| C(12)-C(13)-H(13) | 120.2 |
| C(13)-C(14)-C(15) | 121.0(4) |
| C(13)-C(14)-H(14) | 119.5 |
| C(15)-C(14)-H(14) | 119.5 |
| C(16)-C(15)-C(14) | 118.4(4) |
| C(16)-C(15)-C(18) | 120.7(4) |
| C(14)-C(15)-C(18) | 121.0(4) |

| | |
|---|---|
| C(17)-C(16)-C(15) | 121.3(4) |
| C(17)-C(16)-H(16) | 119.4 |
| C(15)-C(16)-H(16) | 119.4 |
| C(12)-C(17)-C(16) | 118.9(4) |
| C(12)-C(17)-H(17) | 120.6 |
| C(16)-C(17)-H(17) | 120.6 |
| C(15)-C(18)-H(18A) | 109.5 |
| C(15)-C(18)-H(18B) | 109.5 |
| H(18A)-C(18)-H(18B) | 109.5 |
| C(15)-C(18)-H(18C) | 109.5 |
| H(18A)-C(18)-H(18C) | 109.5 |
| H(18B)-C(18)-H(18C) | 109.5 |
| C(8)-N(1)-C(6) | 119.0(3) |
| C(8)-N(1)-C(4) | 109.4(3) |
| C(6)-N(1)-C(4) | 111.2(3) |
| C(8)-O(3)-C(7) | 109.8(3) |
| O(2)-S(1)-O(1) | 120.7(2) |
| O(2)-S(1)-O(5) | 103.48(17) |
| O(1)-S(1)-O(5) | 109.31(18) |
| O(2)-S(1)-C(12) | 110.01(19) |
| O(1)-S(1)-C(12) | 109.4(2) |
| O(5)-S(1)-C(12) | 102.19(18) |

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Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for import.

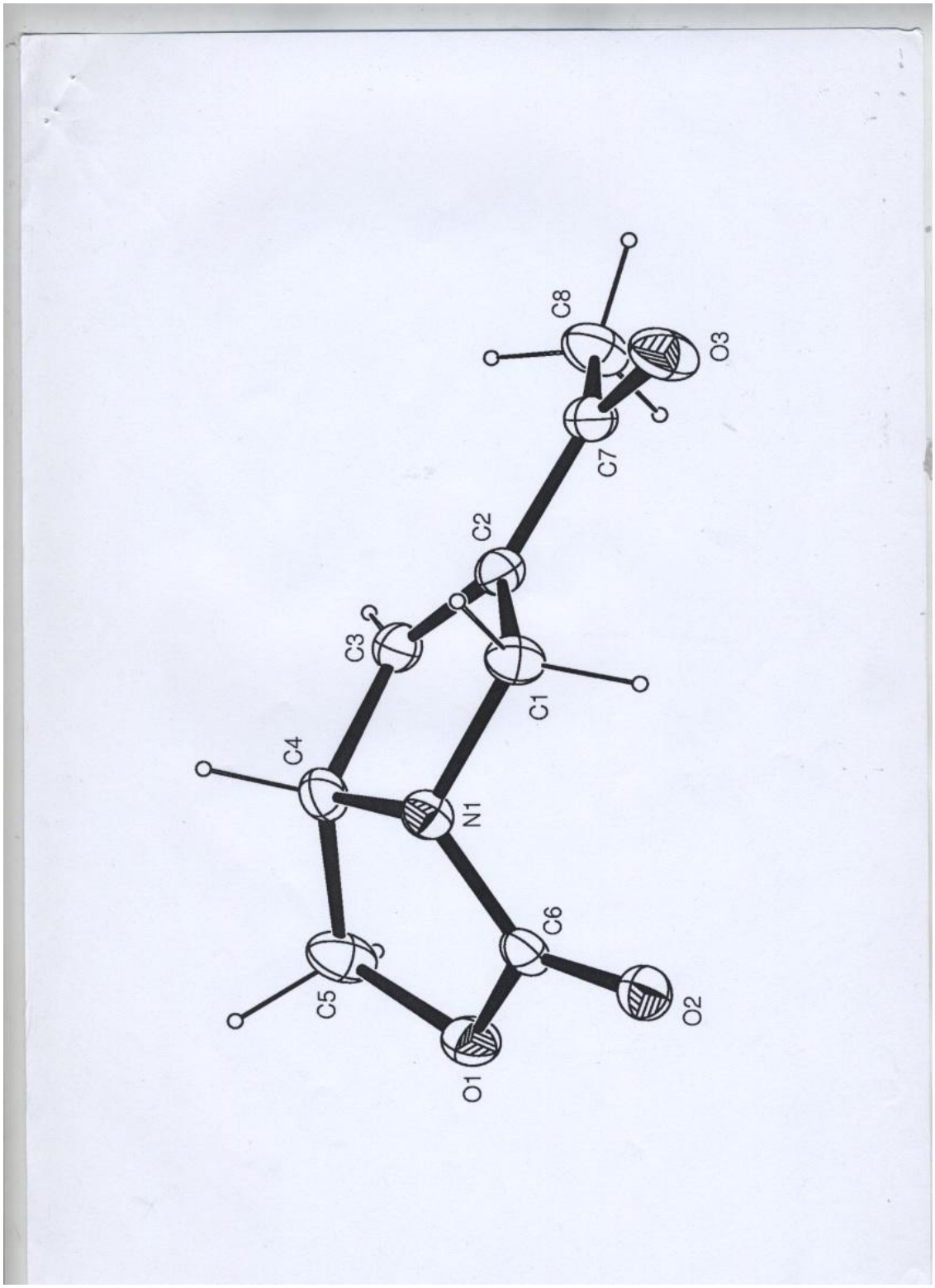
The anisotropic displacement factor exponent takes the form:

-2 pi^2 [ h^2 a*^2 U11 + ... + 2 h k a* b* U12 ]

| | U11 | U22 | U33 | U23 | U13 | U12 |
|---|---|---|---|---|---|---|
| O(5) | 27(1) | 27(2) | 19(1) | -3(1) | 5(1) | -2(1) |
| C(2) | 24(2) | 23(2) | 20(2) | -5(2) | 6(2) | -2(2) |
| C(3) | 30(2) | 18(2) | 24(2) | 2(2) | 4(2) | -4(2) |
| C(4) | 26(2) | 14(2) | 29(2) | -3(2) | 6(2) | 0(2) |
| C(6) | 30(2) | 15(2) | 32(2) | -1(2) | 5(2) | -1(2) |
| C(7) | 31(2) | 19(2) | 47(3) | -4(2) | 3(2) | 0(2) |
| C(8) | 27(2) | 22(2) | 29(2) | 0(2) | 9(2) | -4(2) |
| C(12) | 23(2) | 24(2) | 23(2) | -2(2) | 3(2) | -3(2) |
| C(13) | 33(2) | 36(2) | 22(2) | 4(2) | 8(2) | -2(2) |
| C(14) | 32(2) | 33(2) | 30(2) | 6(2) | 4(2) | 0(2) |
| C(15) | 23(2) | 34(2) | 30(2) | -9(2) | 2(2) | -8(2) |
| C(16) | 29(2) | 36(2) | 25(2) | -5(2) | 9(2) | -9(2) |
| C(17) | 28(2) | 31(2) | 21(2) | 1(2) | 3(2) | -7(2) |

| | | | | | | |
|---|---|---|---|---|---|---|
| C(18) | 35(2) | 42(3) | 41(3) | -9(2) | 9(2) | 1(2) |
| Cl(1) | 41(1) | 40(1) | 20(1) | 1(1) | 7(1) | -9(1) |
| N(1) | 28(2) | 14(2) | 20(2) | -2(1) | 7(1) | 0(1) |
| O(1) | 42(2) | 27(2) | 28(2) | 5(1) | 4(1) | -3(1) |
| O(2) | 40(2) | 35(2) | 20(1) | -7(1) | 2(1) | -1(1) |
| O(3) | 27(2) | 21(2) | 41(2) | -4(1) | -1(1) | -4(1) |
| O(4) | 44(2) | 18(2) | 41(2) | -9(1) | 7(1) | -7(1) |
| S(1) | 29(1) | 24(1) | 19(1) | -2(1) | 3(1) | -4(1) |

Table 5. Torsion angles [deg] for import.


C8
O3
C7
C2
C3
C1
C4
N1
C6
C5
O2
O1

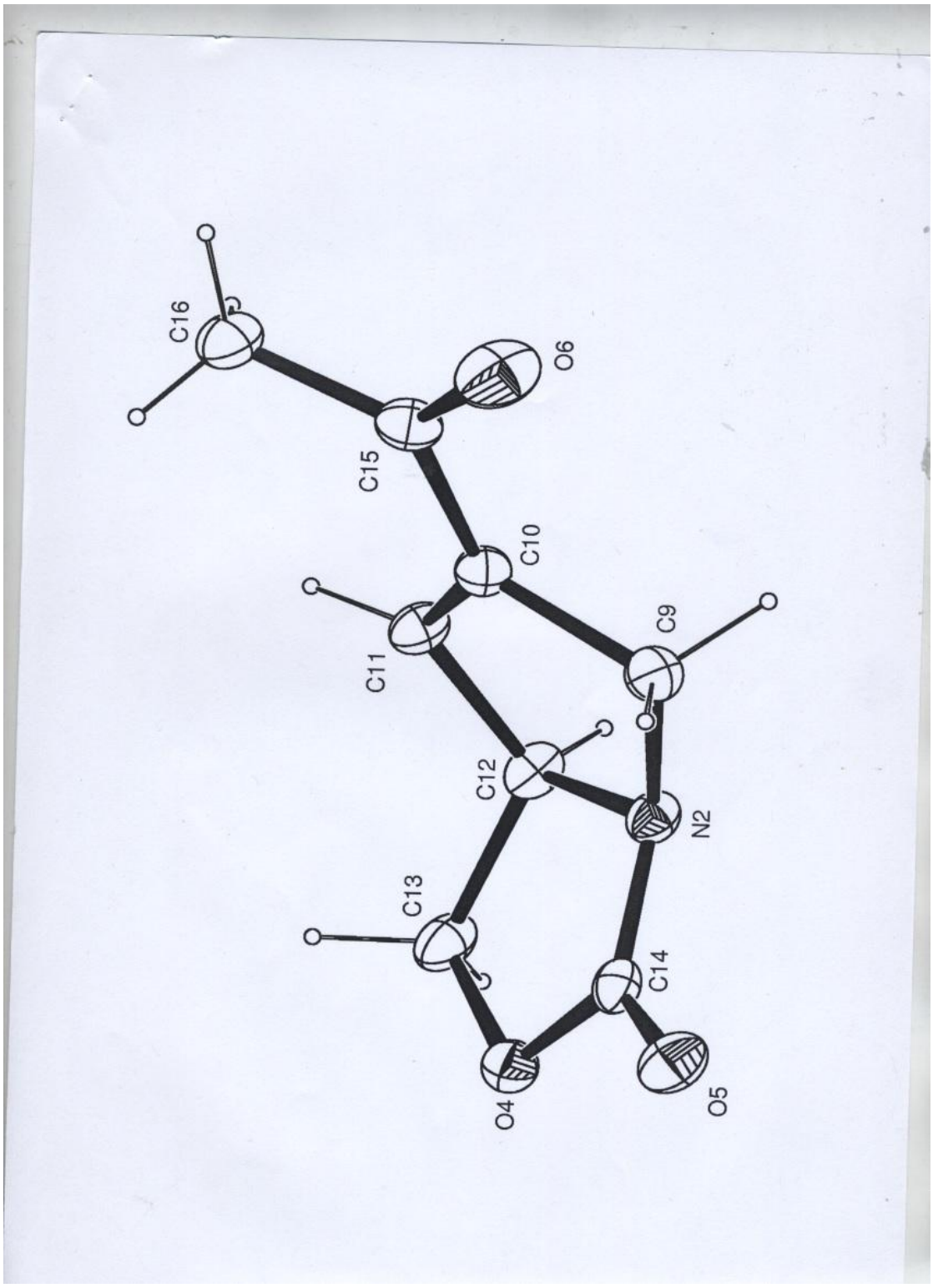

C16
O6
C15
C10
C9
C11
C12
N2
C13
C14
O4
O5

Table 1. Crystal data and structure refinement for $C_8H_9NO_3$.

| | | |
|---|---|---|
| Identification code | jul110 | |
| Empirical formula | C8 H9 N O3 | |
| Formula weight | 167.16 | |
| Temperature | 173(2) K | |
| Wavelength | 0.71070 Å | |
| Crystal system | Monoclinic | |
| Space group | $P\,2_1/c$ (No.14) | |
| Unit cell dimensions | a = 9.6285(7) Å | α= 90°. |
| | b = 14.0538(10) Å | β= 108.345(4)°. |
| | c = 12.1077(5) Å | γ = 90°. |
| Volume | 1555.11(17) Å$^3$ | |
| Z | 8 | |
| Density (calculated) | 1.43 Mg/m$^3$ | |
| Absorption coefficient | 0.11 mm$^{-1}$ | |
| F(000) | 704 | |
| Crystal size | 0.24 x 0.20 x 0.18 mm$^3$ | |
| Theta range for data collection | 3.40 to 26.40°. | |
| Index ranges | -11<=h<=12, -13<=k<=17, -13<=l<=15 | |
| Reflections collected | 10665 | |
| Independent reflections | 3136 [R(int) = 0.058] | |
| Reflections with I>2sigma(I) | 2324 | |
| Completeness to theta = 26.40° | 98.6 % | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 3136 / 0 / 289 | |
| Goodness-of-fit on $F^2$ | 1.032 | |
| Final R indices [I>2sigma(I)] | R1 = 0.043, wR2 = 0.100 | |
| R indices (all data) | R1 = 0.068, wR2 = 0.111 | |
| Largest diff. peak and hole | 0.165 and -0.214 e.Å$^{-3}$ | |

There are two independent molecules in the unit cell with different stereochemistry

Data collection KappaCCD , Program package WinGX , Abs correction not applied

Refinement using SHELXL-97 , Drawing using ORTEP-3 for Windows

Table 2. Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters ($Å^2$x $10^3$) for jul110. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| O(1) | 4840(1) | 929(1) | 9211(1) | 36(1) |
| O(2) | 5582(1) | 1368(1) | 11083(1) | 40(1) |
| O(3) | 1304(2) | 3838(1) | 10676(1) | 44(1) |
| O(4) | 4425(1) | 1002(1) | 4516(1) | 34(1) |
| O(5) | 5463(2) | 1275(1) | 6422(1) | 38(1) |
| O(6) | 9376(2) | 3761(1) | 5840(1) | 50(1) |
| N(1) | 3127(2) | 1240(1) | 10050(1) | 28(1) |
| N(2) | 6845(2) | 1233(1) | 5172(1) | 27(1) |
| C(1) | 2596(2) | 2048(1) | 10579(2) | 31(1) |
| C(2) | 1790(2) | 2636(1) | 9532(1) | 27(1) |
| C(3) | 1643(2) | 2165(1) | 8549(2) | 29(1) |
| C(4) | 2303(2) | 1186(1) | 8803(2) | 32(1) |
| C(5) | 3471(2) | 864(2) | 8270(2) | 41(1) |
| C(6) | 4599(2) | 1201(1) | 10200(1) | 28(1) |
| C(7) | 1235(2) | 3591(1) | 9695(2) | 31(1) |
| C(8) | 636(3) | 4228(2) | 8671(2) | 43(1) |
| C(9) | 7930(2) | 1967(1) | 5710(2) | 30(1) |
| C(10) | 7816(2) | 2623(1) | 4696(1) | 27(1) |
| C(11) | 7003(2) | 2240(1) | 3700(2) | 29(1) |
| C(12) | 6483(2) | 1271(1) | 3898(1) | 30(1) |
| C(13) | 4836(2) | 1075(2) | 3473(2) | 38(1) |
| C(14) | 5588(2) | 1188(1) | 5465(1) | 27(1) |
| C(15) | 8555(2) | 3557(1) | 4871(2) | 31(1) |
| C(16) | 8286(3) | 4222(2) | 3872(2) | 37(1) |

Table 3. Bond lengths [Å] and angles [°] for jul110.

| | |
|---|---|
| O(1)-C(6) | 1.345(2) |
| O(1)-C(5) | 1.448(2) |
| O(2)-C(6) | 1.206(2) |
| O(3)-C(7) | 1.220(2) |
| O(4)-C(14) | 1.354(2) |
| O(4)-C(13) | 1.441(2) |
| O(5)-C(14) | 1.207(2) |
| O(6)-C(15) | 1.224(2) |
| N(1)-C(6) | 1.372(2) |
| N(1)-C(4) | 1.470(2) |
| N(1)-C(1) | 1.472(2) |
| N(2)-C(14) | 1.366(2) |
| N(2)-C(9) | 1.467(2) |
| N(2)-C(12) | 1.471(2) |
| C(1)-C(2) | 1.508(2) |
| C(2)-C(3) | 1.330(2) |
| C(2)-C(7) | 1.480(2) |
| C(3)-C(4) | 1.506(3) |
| C(4)-C(5) | 1.530(3) |
| C(7)-C(8) | 1.490(3) |
| C(9)-C(10) | 1.511(2) |
| C(10)-C(11) | 1.328(2) |
| C(10)-C(15) | 1.476(2) |
| C(11)-C(12) | 1.496(2) |
| C(12)-C(13) | 1.531(3) |
| C(15)-C(16) | 1.486(3) |
| | |
| C(6)-O(1)-C(5) | 110.44(14) |
| C(14)-O(4)-C(13) | 110.38(13) |
| C(6)-N(1)-C(4) | 109.57(14) |
| C(6)-N(1)-C(1) | 117.30(14) |
| C(4)-N(1)-C(1) | 109.77(13) |
| C(14)-N(2)-C(9) | 118.86(14) |
| C(14)-N(2)-C(12) | 109.74(14) |

| | |
|---|---|
| C(9)-N(2)-C(12) | 109.94(13) |
| N(1)-C(1)-C(2) | 102.36(13) |
| C(3)-C(2)-C(7) | 128.97(16) |
| C(3)-C(2)-C(1) | 111.18(15) |
| C(7)-C(2)-C(1) | 119.80(14) |
| C(2)-C(3)-C(4) | 110.66(15) |
| N(1)-C(4)-C(3) | 102.65(13) |
| N(1)-C(4)-C(5) | 102.59(14) |
| C(3)-C(4)-C(5) | 120.25(17) |
| O(1)-C(5)-C(4) | 104.89(14) |
| O(2)-C(6)-O(1) | 122.47(17) |
| O(2)-C(6)-N(1) | 126.83(16) |
| O(1)-C(6)-N(1) | 110.70(14) |
| O(3)-C(7)-C(2) | 118.45(16) |
| O(3)-C(7)-C(8) | 121.83(17) |
| C(2)-C(7)-C(8) | 119.71(16) |
| N(2)-C(9)-C(10) | 102.03(13) |
| C(11)-C(10)-C(15) | 127.66(15) |
| C(11)-C(10)-C(9) | 111.20(15) |
| C(15)-C(10)-C(9) | 121.15(14) |
| C(10)-C(11)-C(12) | 110.80(15) |
| N(2)-C(12)-C(11) | 102.71(13) |
| N(2)-C(12)-C(13) | 102.94(14) |
| C(11)-C(12)-C(13) | 118.24(16) |
| O(4)-C(13)-C(12) | 105.07(13) |
| O(5)-C(14)-O(4) | 121.90(17) |
| O(5)-C(14)-N(2) | 127.49(16) |
| O(4)-C(14)-N(2) | 110.59(14) |
| O(6)-C(15)-C(10) | 118.82(16) |
| O(6)-C(15)-C(16) | 121.85(17) |
| C(10)-C(15)-C(16) | 119.33(15) |

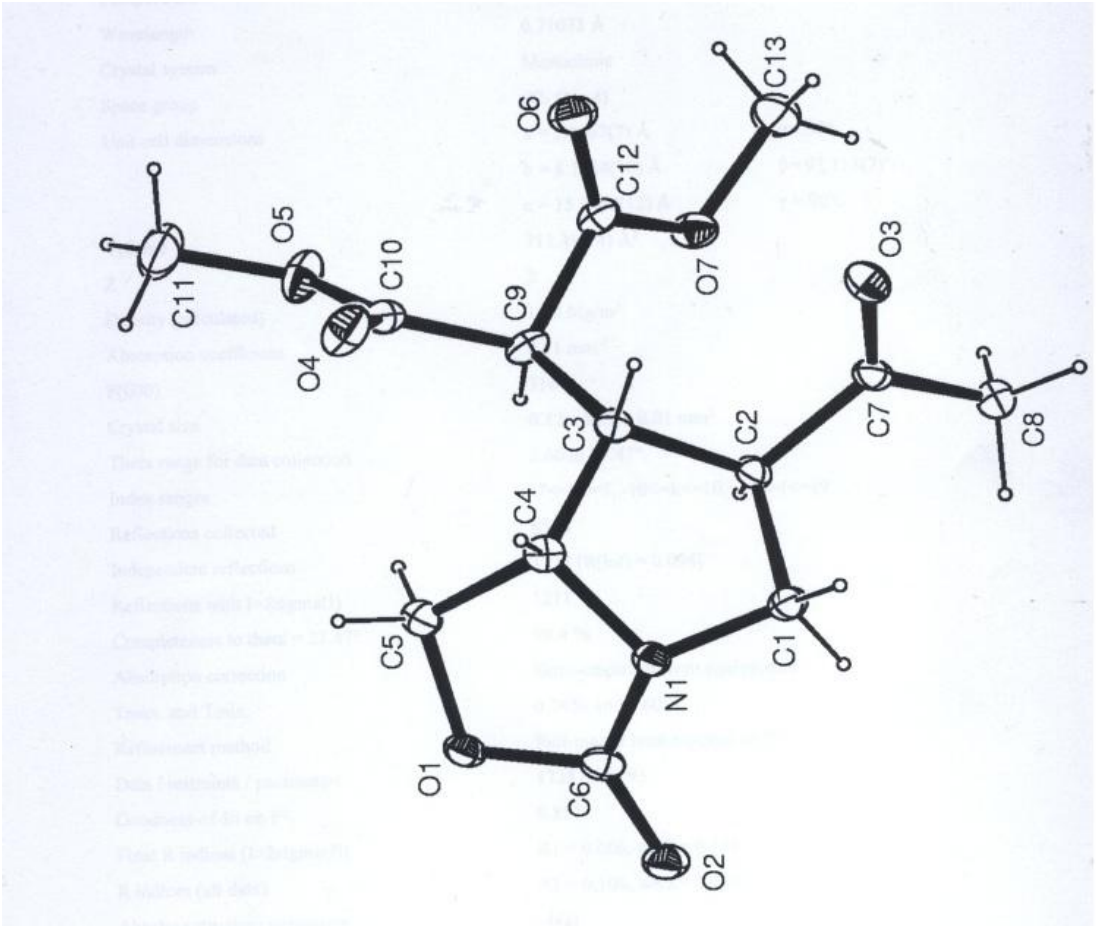

O6
C13
C12
O5
C11
C10
O7
O3
O4
C9
C7
C8
C3
C2
C4
C5
C1
N1
O1
C6
O2

Table 1. Crystal data and structure refinement for RRP210-1.

| | | |
|---|---|---|
| Identification code | may111/2011src0453 | |
| Empirical formula | C13 H17 N O7 | |
| Formula weight | 299.28 | |
| Temperature | 120(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Monoclinic | |
| Space group | $P2_1$ (No.4) | |
| Unit cell dimensions | a = 5.6667(7) Å | α= 90°. |
| | b = 8.1934(10) Å | β= 93.113(7)°. |
| | c = 15.3468(12) Å | γ = 90°. |
| Volume | 711.49(14) Å$^3$ | |
| Z | 2 | |
| Density (calculated) | 1.40 Mg/m$^3$ | |
| Absorption coefficient | 0.11 mm$^{-1}$ | |
| F(000) | 316 | |
| Crystal size | 0.12 x 0.09 x 0.01 mm$^3$ | |
| Theta range for data collection | 3.60 to 27.47°. | |
| Index ranges | -7<=h<=7, -10<=k<=10, -19<=l<=19 | |
| Reflections collected | 8560 | |
| Independent reflections | 1738 [R(int) = 0.098] | |
| Reflections with I>2sigma(I) | 1211 | |
| Completeness to theta = 27.47° | 99.4 % | |
| Absorption correction | Semi-empirical from equivalents | |
| Tmax. and Tmin. | 0.7456 and 0.6098 | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 1738 / 1 / 193 | |
| Goodness-of-fit on $F^2$ | 0.857 | |
| Final R indices [I>2sigma(I)] | R1 = 0.066, wR2 = 0.148 | |
| R indices (all data) | R1 = 0.106, wR2 = 0.179 | |
| Absolute structure parameter | -1(2) | |
| Largest diff. peak and hole | 0.23 and -0.29 e.Å$^{-3}$ | |

Absolute structure cannot be determined reliably

Data collection Bruker-Nonius ROPER CCD camera on \k-goniostat , Program package WinGX , Abs correction MULTISCAN (sadabs); refinement using SHELXL-97 , Drawing using ORTEP-3 for Windows

Table 2. Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters ($Å^2$x $10^3$) for may111. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| O(1) | 3517(6) | 3248(5) | 9056(2) | 25(1) |
| O(2) | 4034(6) | 1468(5) | 10168(2) | 31(1) |
| O(3) | 12646(6) | -120(5) | 7961(2) | 30(1) |
| O(4) | 8024(8) | 4782(5) | 6859(2) | 40(1) |
| O(5) | 5731(7) | 3488(5) | 5846(2) | 37(1) |
| O(6) | 10567(8) | 1491(5) | 5968(2) | 36(1) |
| O(7) | 8724(7) | -715(5) | 6476(2) | 30(1) |
| N(1) | 7141(7) | 2213(5) | 9341(2) | 23(1) |
| C(1) | 8554(9) | 738(7) | 9356(3) | 24(1) |
| C(2) | 8670(8) | 297(6) | 8371(3) | 21(1) |
| C(3) | 8618(8) | 1978(6) | 7906(3) | 20(1) |
| C(4) | 7410(9) | 3168(7) | 8535(3) | 24(1) |
| C(5) | 4878(9) | 3774(7) | 8337(3) | 28(1) |
| C(6) | 4869(8) | 2218(7) | 9572(3) | 24(1) |
| C(7) | 10858(9) | -732(7) | 8233(3) | 23(1) |
| C(8) | 10723(10) | -2503(7) | 8473(3) | 30(1) |
| C(9) | 7470(9) | 1870(7) | 6967(3) | 24(1) |
| C(10) | 7172(9) | 3550(6) | 6568(3) | 24(1) |
| C(11) | 5209(12) | 5045(10) | 5432(4) | 51(2) |
| C(12) | 9093(9) | 890(6) | 6404(3) | 24(1) |
| C(13) | 10362(12) | -1743(9) | 6028(4) | 41(1) |

Table 3. Bond lengths [Å] and angles [°] for may111.

| | |
|---|---|
| O(1)-C(6) | 1.364(6) |
| O(1)-C(5) | 1.445(6) |
| O(2)-C(6) | 1.219(6) |
| O(3)-C(7) | 1.225(6) |
| O(4)-C(10) | 1.195(7) |
| O(5)-C(10) | 1.342(6) |
| O(5)-C(11) | 1.448(8) |
| O(6)-C(12) | 1.203(6) |
| O(7)-C(12) | 1.337(7) |
| O(7)-C(13) | 1.453(7) |
| N(1)-C(6) | 1.354(6) |
| N(1)-C(1) | 1.450(7) |
| N(1)-C(4) | 1.478(6) |
| C(1)-C(2) | 1.559(6) |
| C(2)-C(7) | 1.524(7) |
| C(2)-C(3) | 1.550(7) |
| C(3)-C(9) | 1.550(6) |
| C(3)-C(4) | 1.558(7) |
| C(4)-C(5) | 1.533(7) |
| C(7)-C(8) | 1.499(8) |
| C(9)-C(10) | 1.512(7) |
| C(9)-C(12) | 1.525(7) |
| | |
| C(6)-O(1)-C(5) | 108.8(4) |
| C(10)-O(5)-C(11) | 115.4(5) |
| C(12)-O(7)-C(13) | 115.1(5) |
| C(6)-N(1)-C(1) | 122.0(4) |
| C(6)-N(1)-C(4) | 111.1(4) |
| C(1)-N(1)-C(4) | 111.9(4) |
| N(1)-C(1)-C(2) | 103.3(4) |
| C(7)-C(2)-C(3) | 115.1(4) |
| C(7)-C(2)-C(1) | 109.9(4) |
| C(3)-C(2)-C(1) | 103.9(4) |
| C(9)-C(3)-C(2) | 111.9(4) |

| | |
|---|---|
| C(9)-C(3)-C(4) | 115.8(4) |
| C(2)-C(3)-C(4) | 105.6(4) |
| N(1)-C(4)-C(5) | 101.5(4) |
| N(1)-C(4)-C(3) | 104.8(4) |
| C(5)-C(4)-C(3) | 121.2(4) |
| O(1)-C(5)-C(4) | 106.5(4) |
| O(2)-C(6)-N(1) | 127.5(5) |
| O(2)-C(6)-O(1) | 121.3(4) |
| N(1)-C(6)-O(1) | 111.2(4) |
| O(3)-C(7)-C(8) | 122.3(5) |
| O(3)-C(7)-C(2) | 121.0(5) |
| C(8)-C(7)-C(2) | 116.7(5) |
| C(10)-C(9)-C(12) | 107.9(4) |
| C(10)-C(9)-C(3) | 110.9(4) |
| C(12)-C(9)-C(3) | 108.7(4) |
| O(4)-C(10)-O(5) | 123.8(5) |
| O(4)-C(10)-C(9) | 125.7(4) |
| O(5)-C(10)-C(9) | 110.4(4) |
| O(6)-C(12)-O(7) | 124.4(5) |
| O(6)-C(12)-C(9) | 123.9(5) |
| O(7)-C(12)-C(9) | 111.7(4) |